THE American Journal OF Gastroenterology

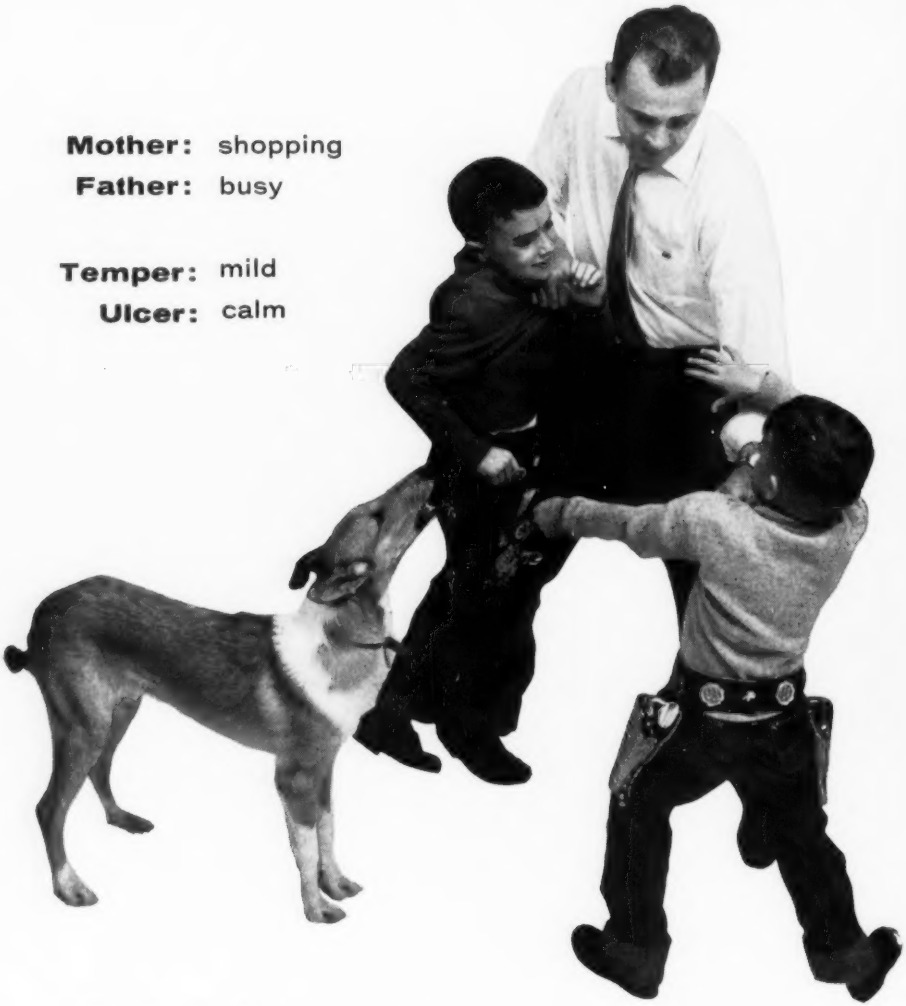
VOL. 33, NO. 3 MARCH, 1960

Twenty-fifth Annual Convention
Philadelphia, Pennsylvania
23, 24, 25, 26 October 1960

Official Publication
AMERICAN COLLEGE
OF GASTROENTEROLOGY

Mother: shopping
Father: busy

Temper: mild
Ulcer: calm



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• calms emotional distress • promotes healing • reduces acid secretion • relieves pain • inhibits gastric motility

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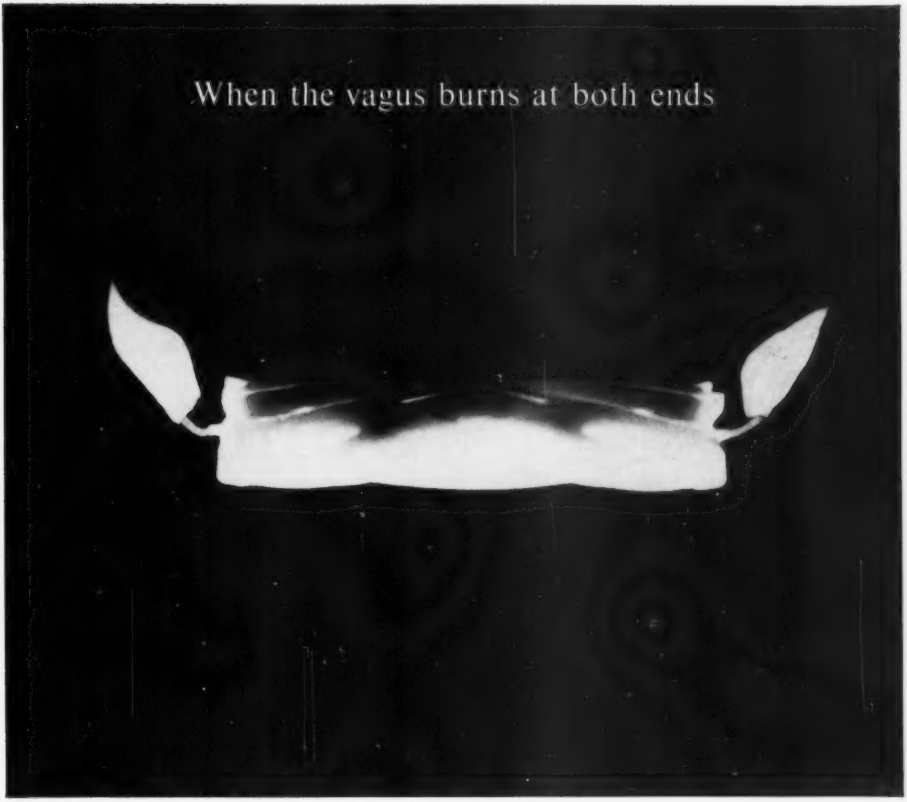

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VOL. 33, NO. 3 MARCH, 1960

THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

contents:

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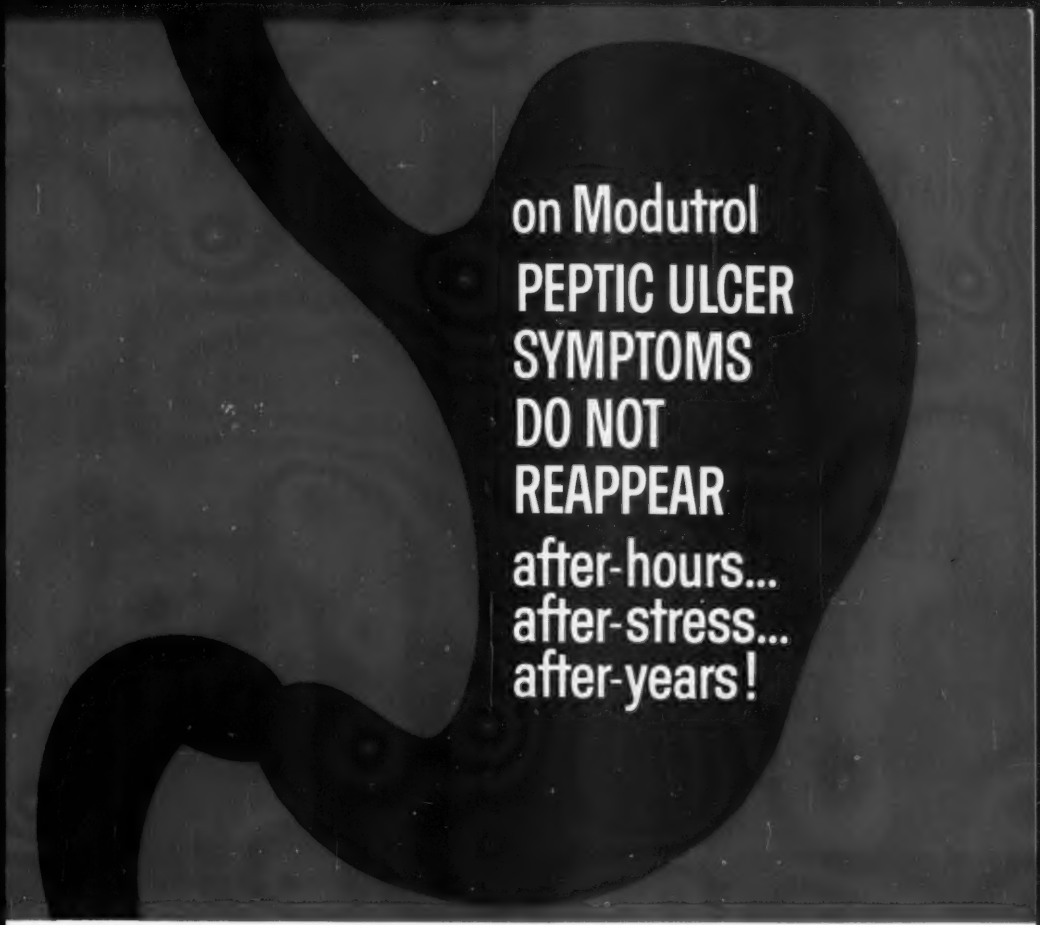

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1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

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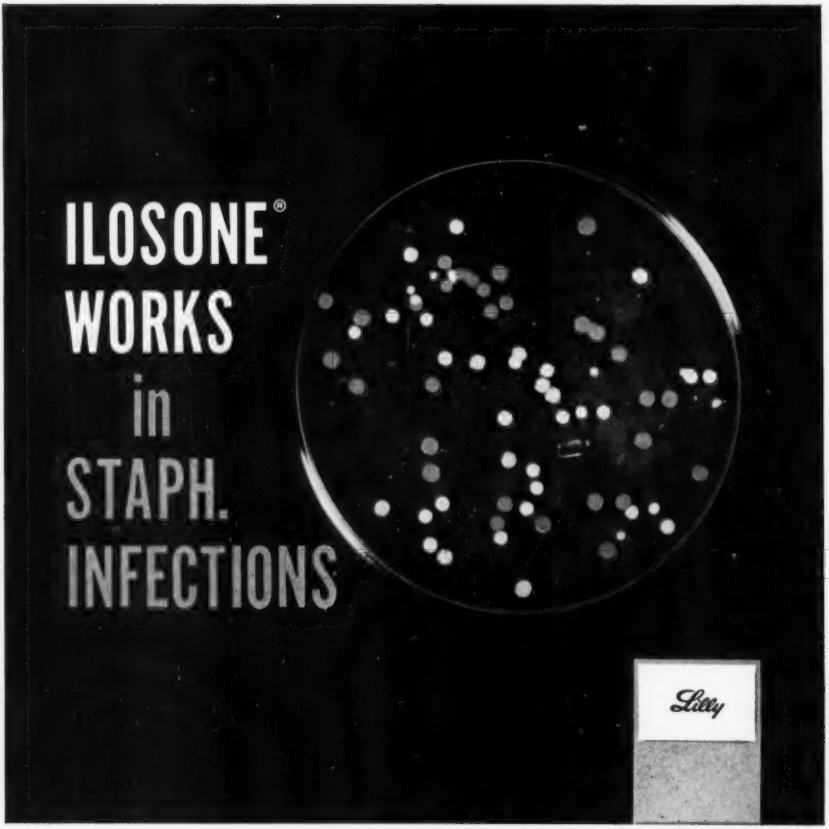

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1. Smith, I. M., and Soderstrom, W. H.: J. A. M. A., *170*:184 (May 9), 1959.

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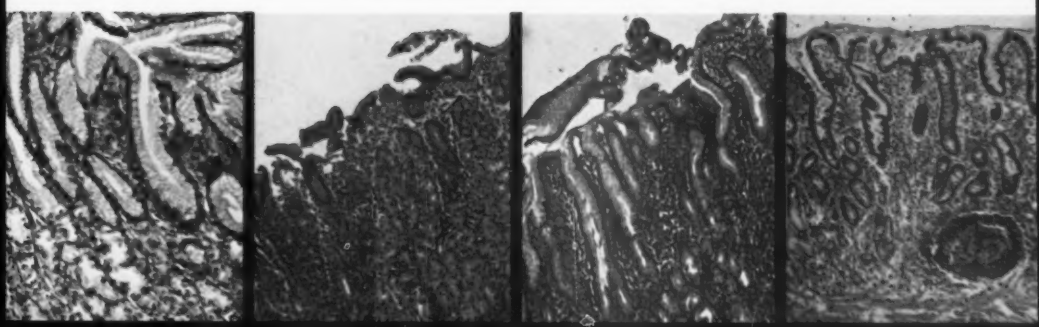
a pathological entity

histologically demonstrable



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Reversible. Glandular pattern, muscularis well preserved.

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Reversible. Irregular distribution of glands. Early intestinalization of surface epithelium. Disruption of muscularis secondary to inflammatory process.

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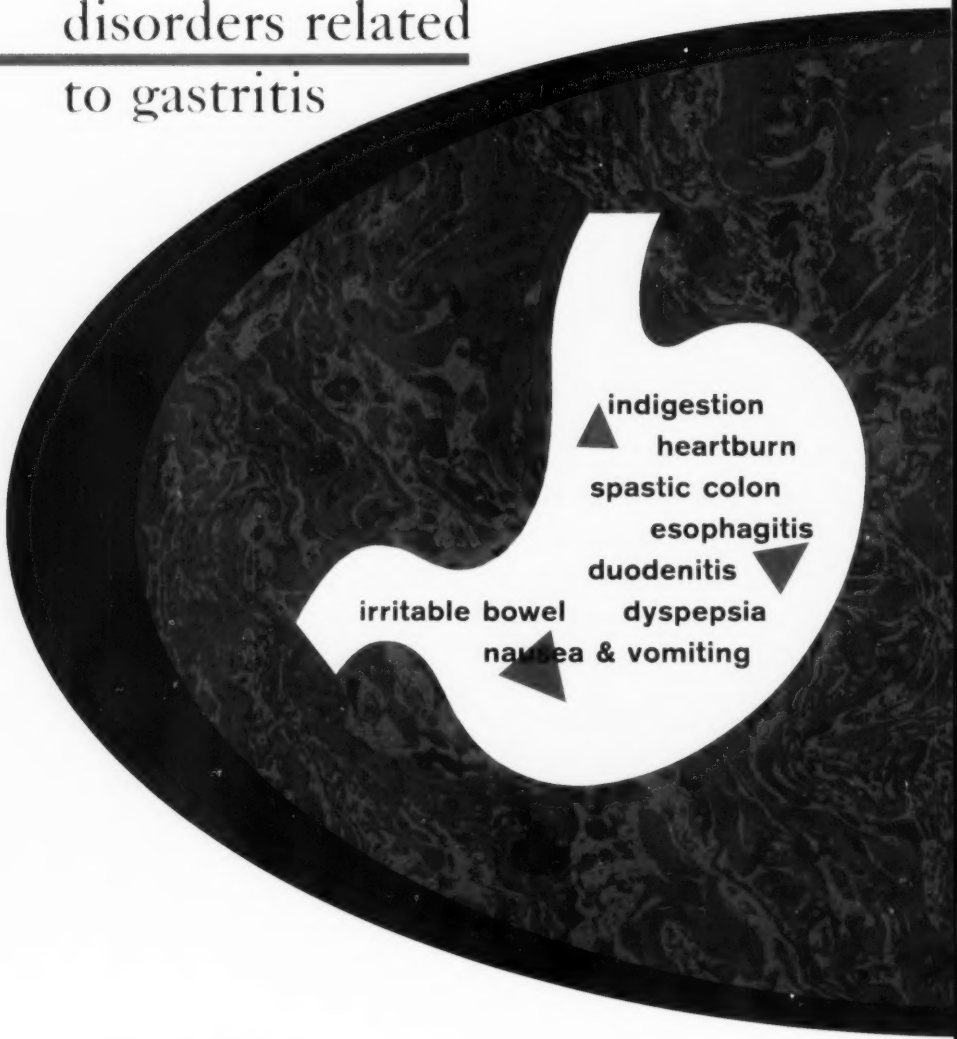
Irreversible. Considerable distortion of glands. Mucous cells indicate conversion to colonic-type tissue. Fragmentation of muscularis.

Microscopic views of gastric biopsies, courtesy of E. Deutsch, M.D., originally published as part of study, 'Chronic Gastritis, Deutsch, E., and Christian, H. J.: J.A.M.A. 169:2012 (Apr. 25) 1959.

disorders related to gastritis



symptoms

Pain - Food - Pain—as opposed to Pain - Food - Relief in peptic ulcer

Persistent, generalized upper abdominal pain—as opposed to localized pain of peptic ulcer

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PAIN

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Oxethazaine in Alumina Gel, Wyeth

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GASTRITIS

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Do not exceed recommended dosage.

Supplied: Bottles of 12 fluidounces.

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Diagnostic Quandaries

Colitis? Gall Bladder Disease?
Chronic Appendicitis?
Rheumatoid Arthritis? Regional Enteritis?

A DISEASE that is frequently overlooked in solving diagnostic quandaries is amebiasis. Its symptoms are varied and contradictory, and diagnosis is extremely difficult. In one study, 56% of the cases would have been overlooked if the routine three stool specimens had been relied on.[1]

Another study found 96% of a group of 150 patients with rheumatoid arthritis were infected by *E. histolytica*. In 15 of these subjects, nine stool specimens were required to establish the diagnosis.[2]

Webster discovered amebic infection in 147 cases with prior diagnoses of spastic colon, psychoneurosis, gall bladder disease, nervous indigestion, chronic appendicitis, and other diseases. Duration of symptoms varied from one week to over 30 years. In some cases, it took as many as six stool specimens to establish the diagnosis of amebiasis.[3]

Now treatment with Glarubin provides a means of differential diagnosis in suspected cases of amebiasis. Glarubin, a crystalline glycoside obtained from the fruit of *Simarouba glauca*, is a safe, effective amebicide. It contains no arsenic, bismuth, or iodine. Its virtual freedom from toxicity makes it practical to treat suspected cases without undertaking difficult, and frequently undependable, stool analyses. Marked improvement following administration of Glarubin indicates pathologically significant amebic infection.

Glarubin is administered orally in tablet form and does not require strict medical supervision or hospitalization. Extensive clinical trials prove it highly effective in intestinal amebiasis.

Glarubin*

TABLETS

specific for intestinal amebiasis

Supplied in bottles of 40 tablets, each tablet containing 50 mg. of glaucarubin.

Write for descriptive literature, bibliography, and dosage schedules.

1. Cook, J.E., Briggs, G.W., and Hindley, F.W.: Chronic Amebiasis and the Need for a Diagnostic Profile, Am. Pract. and Dig. of Treat. *6*:1821 (Dec., 1955).

2. Rinehart, R.E., and Marcus, H.: Incidence of Amebiasis in Healthy Individuals, Clinic Patients and Those with Rheumatoid Arthritis, Northwest Med., *54*:708 (July, 1955).

3. Webster, B.H.: Amebiasis, a Disease of Multiple Manifestations, Am. Pract. and Dig. of Treat. *9*:897 (June, 1958).

*U.S. Pat. No. 2,864,745

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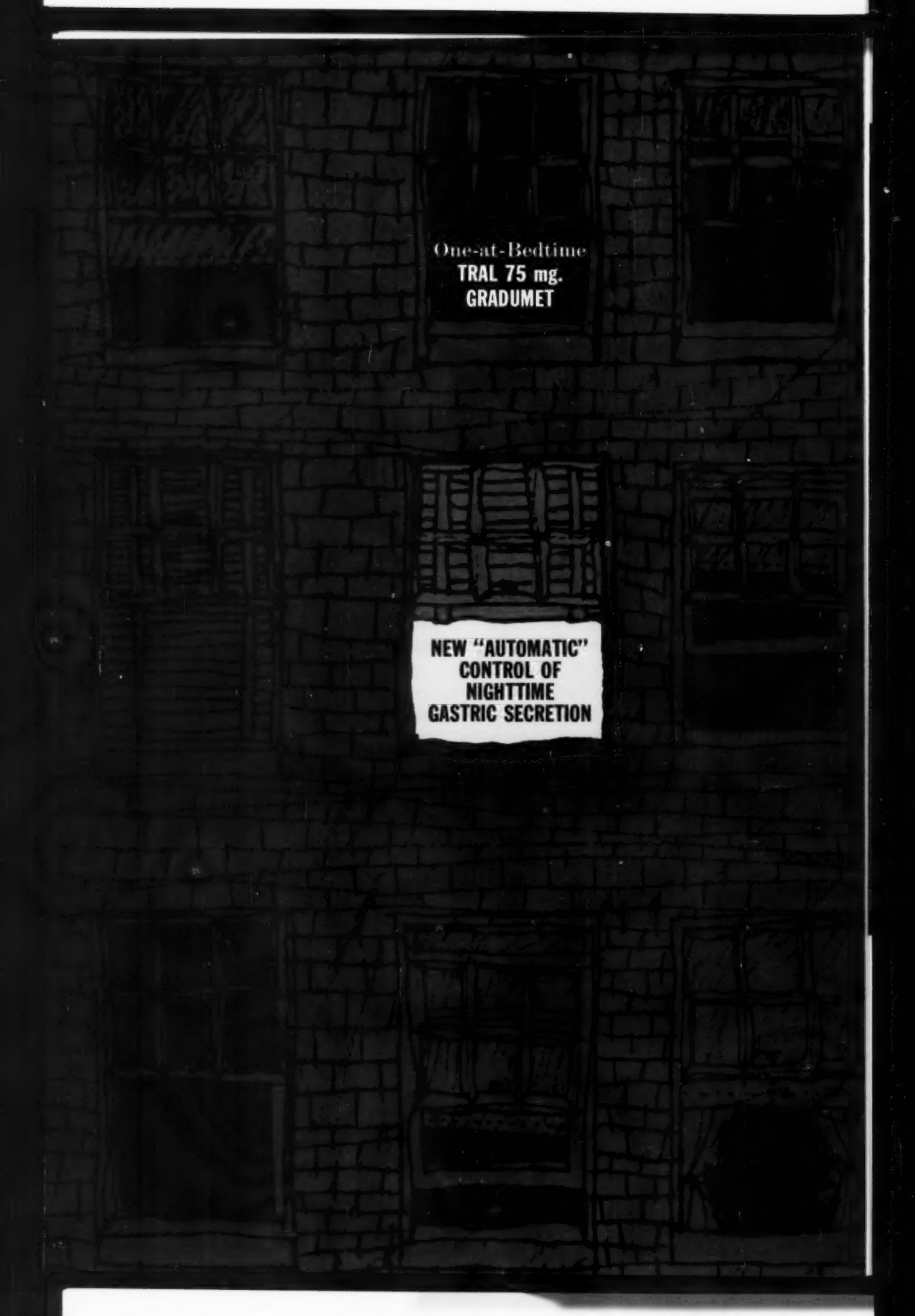
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GASTRIC SECRETION

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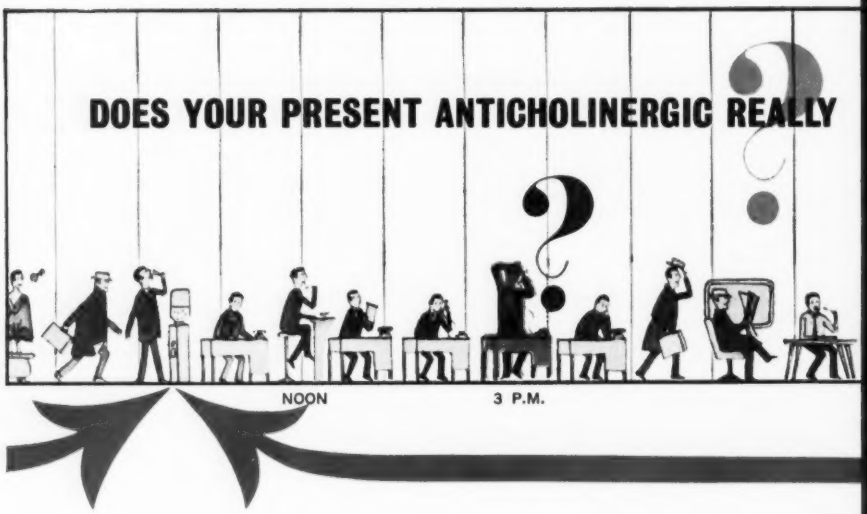


The test—you might say the acid test—of an anticholinergic is simple: will it protect your patient from hyperacidity around the clock, **even while he sleeps.** The weakness of t.i.d. or q.i.d. preparations is well recognized; but even some "b.i.d." encapsulations may be unreliable. McHardy, for instance, found a "widely variable duration of action, definitely less than that anticipated" in the "sustained," "delayed," and "gradual release" anticholinergics he studied.[1]

COMPARE THE DATA ON ENARAX . . . the new combination of an **inherently** long-acting anticholinergic (oxyphencyclimine) and Atarax, the non-secretory tranquilizer. Note the effectiveness of oxyphencyclimine:

OBSERVE THE OXYPHENCYCLIMINE REPORTS . . .

McHardy: "[Oxyphencyclimine] has proved to be an excellent sustained-action anticholinergic in our study of this agent over a period of eighteen months."[1]

Kemp: ". . . for the majority of patients, one tablet every 12 hours provided adequate control. This characteristic long action . . . may constitute an advantage of this drug as compared to coated 'long-acting' preparations of other compounds."[3]

Add Atarax to this 12-hour anticholinergic. The resulting combination—ENARAX—now gives relief from emotional stress, in addition to a reduction of spasm and acid. Atarax does not stimulate gastric secretion. No serious adverse clinical reaction has ever been documented with Atarax.

LOOK AT THE RESULTS WITH ENARAX[4,5]:

Does the medication you now prescribe assure you of all these benefits? If not, why not put your next patient with peptic ulcer or G.I. dysfunction on therapy that **does.**

ENARAX®

(oxyphencyclimine plus ATARAX®)

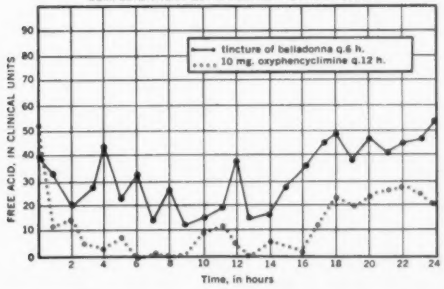
A SENTRY FOR THE G.I. TRACT

PROVIDE CONTINUOUS CONTROL OF ACID SECRETION?

MIDNIGHT 2 A.M.

"Prolonged periods of achlorhydria" after 10 mg. oxyphencyclimine q. 12 h.[1]

MEAN GRAPH OF GASTRIC ACIDITY IN 4 PATIENTS RECEIVING COMPLETE THERAPEUTIC REGIMEN · 24-HOUR STUDY



Clinical Diagnosis: Peptic Ulcer—Gastritis—Gastroenteritis—Colitis—Functional Bowel Syndrome—Duodenitis—Hiatus Hernia (symptomatic)—Irritable Bowel Syndrome—Pylorospasm—Cardiospasm—Biliary Tract Dysfunctions—and Dysmenorrhea.

Clinical Results: Effective in over 92% of cases.

As for Safety: "Side reactions were uncommon, usually no more than dryness of the mouth. . . ."[4]

Each ENARAX tablet contains:

Oxyphencyclimine HCl ..... 10 mg.
Hydroxyzine (ATARAX®) ..... 25 mg.

Dosage: One-half to one tablet twice daily—preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy and with ophthalmological supervision only in glaucoma.

Supplied: In bottles of 60 black-and-white scored tablets.

References: 1. McHardy, G., et al.: J. Louisiana M. Soc. 111:290 (Aug.) 1959. 2. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois, in press. 3. Kemp, J. A.: Antibiotic Med. & Clin. Therapy 6:534 (Sept.) 1959. 4. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959. 5. Data in Roerig Medical Department files.

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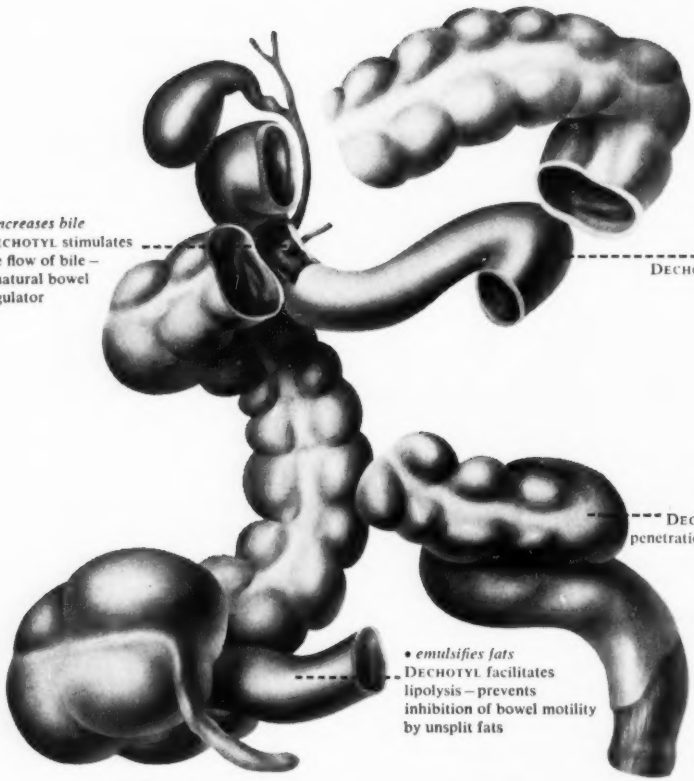

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well tolerated...gentle transition to normal bowel function

Recommended to help convert the patient – naturally and gradually – to healthy bowel habits. Regimens of one week or more are suggested to assure maintenance of normal rhythm and to avoid the repetition of either laxative abuse or constipation.

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Contraindications: Biliary tract obstruction; acute hepatitis.

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*AMES T.M. for trapezoid-shaped tablet.

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VOLUME 33 MARCH, 1960 NUMBER 3

EXFOLIATIVE CYTOLOGY STUDIES OF GASTRIC LAVAGE*

DEAN L. MOYER, M.D.†
and
L. J. ZELDIS, M.D.†
Los Angeles, Calif.

During the past decade there has been increasing use of exfoliative cytological technics by the gastroenterologist. Cytologic methods have developed into helpful adjuncts to clinical examination, radiologic diagnosis, and gastroscopy. The technics for collection of specimens from the esophagus and stomach are associated with minimal trauma and are uncomplicated enough to be utilized at the bedside and in the physician's office.

Historically the methods are not entirely current in gastroenterology. During the 19th century European investigators made use of aspirated cells and tissue fragments in the diagnosis of gastrointestinal carcinoma. The zenith of their efforts was recorded in 1909 by Marini, who was able to diagnose 32 out of 37 gastric carcinomas from the appearance of unstained cells following thorough lavage[1]. His methods for collecting material and his interpretations of the malignant cells are essentially the same as we use today. His success reflects an obvious understanding of the need for meticulous technic in collection and preparation of specimens. The method, however, fell into disuse during the following decades, and it was not until Papanicolaou applied superior staining methods that exfoliative cytology was again developed as a useful diagnostic aid in gastroenterology.

A number of modifications of older technics for the collection of freshly exfoliated cells from the gastric mucosa have been devised during the past ten years. Methods include simple gastric lavage or lavage with solutions of enzymes such as papain[2] or chymotrypsin[3] to facilitate exfoliation of superficial cells. Use

*Read before the 24th Annual Convention of the American College of Gastroenterology, Los Angeles, Calif., 21, 22, 23 September 1959.

†Department of Pathology, School of Medicine, University of California, Los Angeles, Calif.

of an abrasive balloon[4], brush[5], or sponge[6] have all yielded gratifying results to those who have become skilled in a particular technic.

Methods of Specimen Collection

In our experience, simple gastric lavage, carefully and thoroughly performed, has yielded positive results in all cases in which mechanical or enzymatic methods have done so. Best results are obtained when effort is directed toward minimizing cell digestion and avoiding contamination of gastric contents by food, either solid or liquid.

Care must be taken to cleanse the stomach before specimens are obtained for examination. It is desirable that the patient fast for 8 to 12 hours before the gastric analysis. Although this fasting specimen should be examined, it usually is of value only in screening for malignant squamous cells, particularly from esophagus or pharynx, since these undergo degeneration more slowly than the more fragile gastric cells. Cleansing procedures also eliminate other foreign materials, such as vegetable cells, oral medication, buccal and respiratory cells, and macrophagic "dust" cells. In patients with partial or complete gastrointestinal obstruction, a complete aspiration with multiple saline lavages must be performed to rid the stomach of the ever-present detritus.

When the aspiration tube is situated at the site thought most likely to contain a malignancy or abnormality, a saline wash of the area is performed. In lavaging the esophagus where an obstruction is present in the lower third, a gentle wash using from 10 to 50 ml. of normal saline solution is repeated several times. In a duodenal intubation, a wash of 25 ml. of normal saline is followed by a secretin (1 unit/kg.) injection and amyl nitrite inhalation and several aspirations and saline washes are repeated in 10 minutes. This is essentially the method described by Raskin and co-workers[7]. In the recovery of specimens from the stomach, several saline washes of 100 to 250 ml. each are introduced under mild pressure creating a modified jet stream. During this time the tube is moved slowly from the fundus to antrum to attempt to reach various portions of the stomach. Slightly chilled saline is used and is withdrawn immediately. The saline wash and aspirations may be followed by introduction of a buffered chymotrypsin solution which is allowed to remain for 10 minutes with rotation of the patient. In all of our positive cases, however, malignant cells have been clearly identified in the saline wash as well as in the chymotrypsin procedure. If the specimen is allowed to remain at room temperature for any length of time it is found that the cells in the chymotrypsin specimen show more degeneration than those in the saline specimen. For these reasons the chymotrypsin wash has been eliminated from our routine procedure.

Following the aspiration of upper gastrointestinal contents the aspirate is placed in iced petri dishes. The petri dishes are then placed on a white background and any blood streaked particles or mucus threads are smeared on slides

and fixed immediately in a 1:1 mixture of absolute ether and 95 per cent alcohol. The petri dishes are then placed over a black background and the white fragments usually containing cells and tissue fragments are smeared and immediately fixed. The remainder of the specimen is spun in iced 50 ml. centrifuge tubes in a cold (3° C.) centrifuge for 5 minutes at 3,000 rpm. The residue is smeared with a loop and fixed immediately.

Results

In the cytologic studies presented here, examinations were made of 105 specimens obtained by gastric lavage from 78 patients. All were being studied in the hospital or outpatient department of the U.C.L.A. Medical Center for gastrointestinal complaints.

TABLE I

Exfoliative Cytology of Gastric Lavage

Patients Categorized by Tissue Diagnosis

Patient group	Number of patients	Category
A	18	*Tissue diagnosis* of malignancy of esophagus or stomach
B	17	*Tissue diagnosis* of benign lesion of stomach or small intestine or malignancy elsewhere
C	43	*Clinical diagnosis* of benign lesion of upper gastrointestinal tract

The majority (55 per cent) of these patients had a roentgen diagnosis of a filling defect of the stomach. Three patients had a clinical and roentgenographic diagnosis of carcinoma before cell studies were performed; others showed radiographic evidence of large rugal folds, gastritis, or upper abdominal masses. The most frequent symptomatology included abdominal pain and gastrointestinal bleeding.

The 78 patients studied were grouped according to associated tissue diagnosis as summarized in Table I. In 18 of these (patient group A), a malignant lesion of the esophagus or stomach was demonstrated. In 17 (patient group B), either benign lesions of the upper gastrointestinal tract, or malignancies which did not involve the esophagus or stomach were found. In the remaining 43 cases (patient group C), no tissue was obtained for histologic study because surgical indications were not present in the face of clinical, radiographic, and cytologic evidence of benign lesions and because no patients of this group came to autopsy.

Table II illustrates the cytology findings in the 18 patients (group A) with autopsy or surgical tissue diagnoses of a malignancy of the upper gastrointestinal tract. In 10 patients with gastric carcinoma, lavage specimens contained cells consistent with malignancy (smears Class IV or V). A single lavage was performed in each of these cases. Two other patients with gastric carcinoma exhibited cells suggestive of malignancy (smears Class III), a single lavage also having been performed in each of these cases. One patient having an esophageal carcinoma exhibited Class V cells in a lavage of the obstructed esophagus. Another patient ultimately diagnosed as having metastatic melanoma of the stomach showed Class V cells in the gastric lavage specimen. This diagnosis was reported at the time of cytologic study because of the presence of large amounts

TABLE II

EXFOLIATIVE CYTOLOGY OF GASTRIC LAVAGE

CYTOLOGIC CLASSES IN PATIENT GROUP A WITH MALIGNANCY OF ESOPHAGUS OR STOMACH

Histologic diagnosis	Cytology class	Number of patients	Number of specimens
Gastric carcinoma	IV-V	10	10
Gastric carcinoma	III	2	2
Gastric carcinoma	I-II	3	5
Esophageal carcinoma	V	1	1
Metastatic melanoma in stomach	V	1	1
Lymphosarcoma of stomach	III	1	1
Total		18	20

of brown and black cytoplasmic pigment within atypical cells. One patient with a lymphosarcoma involving the stomach showed numerous lymphoid cells in the lavage specimen. Stained by Papanicolaou and Giemsa technics these cells exhibited a degree of nuclear atypism not found in normal lymphocytes. The smear was grouped in Class III and reported as suggestive of lymphoma.

Three patients ultimately proven by tissue diagnosis to have gastric carcinoma failed to exhibit cells suggestive of or consistent with malignancy in a total of 5 gastric lavages. Each of these patients had a clinical and radiographic diagnosis of gastric carcinoma before the lavages were performed. In order to study further these three cases of false negative gastric cytology, multiple saline washes were performed on the resected stomachs immediately following surgery.

The aspirated fluid was processed for cytologic study in the usual manner. Slides were pressed onto the gastric mucosa and immediately fixed. These examinations yielded no recognizably malignant cells. The histological study of the resected gastric specimens suggested possible explanations of the negative gastric washings. Two of the specimens were scirrhous carcinomas and the third was a large ulcerating adenocarcinoma with a thick coagulated membrane covering the surface of the tumor. The malignant cells of the scirrhous carcinoma lay primarily in the lamina propria and muscularis, and only rarely extended up into the deeper portions of the mucosa. In the advanced ulcerated carcinoma, gross examination of the stomach showed a tenacious membrane of fibrin and

TABLE III

EXFOLIATIVE CYTOLOGY OF GASTRIC LAVAGE

CYTOLOGIC CLASSES IN PATIENT GROUP B WITH NO MALIGNANCY OF ESOPHAGUS OR STOMACH

Histologic diagnosis	Cytology class	Number of patients	Number of specimens
Gastric ulcer	III	2	3*
Gastric ulcer	I-II	5	6
Hypertrophic gastritis	I-II	1	1
Malignancy not involving gastrointestinal tract	I-II	7	7
Infarction ileum and jejunum	I-II	1	1
Normal stomach	I-II	1	1
Total		17	19

*Including one repeat specimen of Class I.

debris overlying the ulcerated portion of the tumor. The membrane was dislodged only with difficulty by directing a jet stream of saline on the tumor. It may be considered likely that the preoperative lavage found the membrane impenetrable. Subsequent histologic study also suggested that only a deep biopsy would in these cases have obtained malignant cells sufficiently well-preserved for study. Failure to procure malignant cells from these types of carcinoma has been observed previously[8,9].

Table III summarizes the cytology findings in the 17 patients (group B) in whom no malignancy was found in the esophagus or stomach on autopsy, biopsy, or surgical resection. Single lavage specimens from each of two patients who were subsequently proved to have benign gastric ulcers were grouped in

Class III. A repeat lavage was done in one of these cases and yielded a Class I smear. The chief abnormality in these two Class III specimens was an "active" hyperchromatic nuclear atypism. Some information concerning the source and significance of the atypical cells was obtained by performing, at the time of surgery, *in vitro* gastric lavages on the partial gastrectomy specimens. Some atypical cells quite similar to those in the preoperative specimens were recovered. When a glass slide was wiped across the mucosa adjoining the ulcerated area and tissue blocks taken of the area, the regenerating mucosal cells exhibited varying degrees of nuclear enlargement and hyperchromatism. Comparison in retrospect with the original preoperative lavage specimens clearly indicated that misinterpretation of these cells was responsible for the false positive reports.

TABLE IV

EXFOLIATIVE CYTOLOGY OF GASTRIC LAVAGE

CYTOLOGIC CLASSES III, IV, AND V OF PATIENT GROUPS A AND B COMPARED WITH TISSUE DIAGNOSES

Cytologic class	Tissue diagnosis	Number of cases
IV or V	Gastric carcinoma	10
V	Esophageal carcinoma	1
V	Metastatic melanoma	1
III	Gastric carcinoma	2
III	Lymphosarcoma	1
III	Benign gastric ulcer	2

An additional five patients in whom the resected stomachs demonstrated benign gastric ulcers are shown in Table III to have had Class I or II cells in one or more preoperative gastric lavages.

Of the other patients listed in Table III as having gastric lavage specimens of Class I or II, seven had clinical diagnoses of malignancy and symptoms suggesting the possibility of upper gastrointestinal tract involvement. All seven of these patients ultimately came to autopsy and were found to have malignancies of the lung, pancreas, or large bowel, in no case directly involving the stomach or esophagus.

The remaining three patients in whom gastric cytology of Class I-II is listed in Table III showed benign conditions on subsequent histologic study. One patient at laparotomy showed enlarged gastric rugal folds consistent with the impression of hypertrophic gastritis and biopsy confirmed this diagnosis. A sec-

ond patient showed an infarcted ileum and jejunum at laparotomy and tissue diagnosis was characteristic of this condition. The third patient was found at autopsy to have an hiatus hernia and the stomach was grossly and histologically normal.

Table IV summarizes the final histologic diagnoses in the 17 patients with cytologic studies suggestive of or consistent with malignancy (cytology Classes III, IV, and V). *No false positive cytologic smears of Classes IV or V were encountered in this small study.* Frankly malignant cells were present in the total of 12 lavage specimens from the 10 patients with gastric carcinoma and from the 2 patients with an esophageal carcinoma and a metastatic melanoma. Of the five patients listed in Table IV in whom Class III cytology was demonstrated, two were ultimately found to have carcinomas and one a lymphosarcoma of the stomach. The two cases of carcinoma exhibiting Class III cytology were later found on histologic study to be quite well-differentiated as compared to the carcinomas demonstrating Class IV and V cytology.

Comment

As in other studies thus far reported, the problem in differential diagnosis most frequently presented to the cytologist in the examination of this series of patients was to determine the presence or absence of malignant cells in patients in whom major manifestations of significant gastric lesions had already been recognized. This is a special category of patients in which there is a great need for additional reliable diagnostic methods. Smith and Jordan[10] have reported, for example, that in 600 patients with a diagnosis of benign gastric ulcer made on an initial visit, subsequent clinical, roentgenological, and surgical studies yielded a diagnosis of carcinoma in 9.3 per cent.

In the group of 78 patients reported here 64 patients or 86 per cent had roentgenographic evidence of an upper gastrointestinal lesion and 43 patients or 55 per cent were known to have an ulcerating lesion of the stomach or duodenum. On such a background exfoliative cytology studies are of much value. The presence in gastric lavage specimens of cells sufficiently abnormal to be designated Class IV or Class V in the Papanicolaou classification[11] may be regarded as a highly reliable indication of malignancy. Failure to identify malignant cells in washings from patients with other findings suggestive of malignancy must be considered as nondefinitive and as possibly representing false negative cytology. Three of 18 proved cases of malignancy yielded false negative cytology in the series reported here. These were found to be associated with one unusually large malignant ulcer and with two scirrhous carcinomas presenting roentgenographic deformities characteristic of *linitis plastica.*

In this study, Class III cytology (cells suggestive of malignancy) was found in three of 18 patients with proved malignancy. False positive cytology of Class III was reported in 2 patients of a total of 60 in whom the final pathologic or

clinical diagnosis was of a benign lesion. For the present the degrees of cytologic abnormality encompassed in Class III should be considered equivocal and be carefully evaluated in conjunction with clinical and radiologic findings. It may be anticipated that further study, particularly of the cytologic characteristics of regenerating gastric mucosa in the margins of benign ulcers, will reduce but perhaps not eliminate false positive interpretations.

It is not to be anticipated that gastric exfoliative cytology will develop on a basis comparable to the routine vaginal screening which is yielding dramatic results in identification of cases of possible carcinoma of the cervix. It is, on the other hand, reasonable to predict that if exfoliative cytology is to find uniquely useful application in gastroenterology it will be in the study of that large number of patients with ill-defined complaints in whom other presently available diagnostic methods fail to differentiate malignant and benign lesions. A few case reports are available to illustrate the possible effectiveness of the method in recognition of early lesions[8,12,13]. Evaluation must ultimately be based on studies including larger numbers of patients with less well-defined evidence of gastric lesions. A major improvement of the dreary prognosis of gastric carcinoma may result if earlier diagnosis of polypoid and of superficial spreading lesions can be accomplished. In this connection, gastric exfoliative cytology may prove helpful in the management of pernicious anemia patients, in whom the incidence of carcinoma has been clearly shown to be increased[14]. Periodic cytology study in such patients may lead to occasional recognition of an early superficial polypoid carcinoma.

Comment is indicated on the single case of lymphosarcoma of the stomach which is included in this study. Gastric washings in this case were shown to contain cells recognizable as lymphocytes and with degrees of atypism suggestive of malignancy. It is to be expected, however, that not all lymphomas will desquamate cells with frankly malignant characteristics. To the cytologist such cases will usually be presented as problems in the distinction between lymphomas and hypertrophic gastritis. Use of the Giemsa stain in addition to usual staining methods will be of value in this problem.

Summary

Results of cytologic examination of 105 gastric lavage specimens from 78 patients with major gastrointestinal symptoms and clinical findings are presented. Cells suggestive of or consistent with malignancy were identified in 15 of 18 patients in whom a histologic diagnosis of malignancy of the esophagus or stomach was subsequently made.

Three instances of false negative cytology were encountered. Two of these were found to be associated with scirrhous gastric carcinomas and one with an ulcerating carcinoma of the stomach which was covered by a pseudomembrane.

Two instances of false positive cytology of Class III (cells suggestive of malignancy) were found to be associated with regenerating gastric mucosa in the margins of benign ulcers.

Exfoliative cytology is a useful adjunct to clinical and roentgenographic study of patients with major upper gastrointestinal symptoms and clinical findings suggestive of possible malignancy. Further evaluation of the procedure in patients with less well-defined clinical abnormalities is needed to determine whether it may contribute to earlier diagnosis of gastric carcinoma.

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NEEDLE BIOPSY OF THE LIVER IN INFANCY AND EARLY CHILDHOOD*

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Jaundice and hepatomegaly! In these few words may be summarized the entire history and physical manifestations of the diseases of the liver in infancy and early childhood. Other signs may accompany these but they are of the most general nature, i.e., fever, anorexia, weight loss, etc. and are of little value in differential diagnosis. The similarities in the appearances of the various diseases of the liver in children is, to some extent, understandable because of the absence of the patient's subjective description of the illness. More difficult to comprehend, however, is the failure of the usual tests of hepatic function to show predictable alterations even in the face of obvious hepatic disease. For example, in some patients with proven congenital absence of the biliary tree the entire battery of liver function tests has been noted to be normal. Occasionally these patients even have periods during which jaundice is not clinically evident. Similarly children with demonstrably rapidly progressive cirrhosis usually manifest no signs of hepatic disease, other than hepatomegaly, throughout most of the course of their disease, such signs becoming apparent only in the terminal stages.

Because of the similarity in clinical appearances of all hepatic diseases in infancy and because of the lack of help that can be gained from clinical laboratory studies, the pediatricians' dilemma is evident. With the introduction of the technic of needle biopsies a means of differentiating many of these diseases is available and it is therefore somewhat surprising that needle biopsy of the liver is still relatively infrequently utilized in the pediatric age group. Only 3 reports[1-3] on its general use in pediatrics have been published, although it is regularly employed in the investigation of certain specific diseases[4-8]. In none of these reports, which cover several thousand biopsies, have any deaths or complications of the procedure been noted. It is the purpose of this presentation to demonstrate the practicability of needle biopsy in infancy and childhood as well as to present the range of diseases of the liver to which the child is susceptible together with some indication of their frequency.

Technic

A standard Vim-Silverman biopsy needle is employed. In all patients a transabdominal approach is used. In older patients (over 1 year) a barbiturate sedative is given one-half hour prior to the procedure, but in infants the relaxa-

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tion obtained by allowing them to nurse a bottle during the operation is sufficient. The infants are restrained by strips of adhesive tape over the chest and pelvis and assistants hold the arms and thighs. After infiltration of the abdominal wall by a local anesthetic, a small incision in the skin is made to facilitate introduction of the needle. After the needle with the solid stylette is introduced into the liver it is held in the thumb and index finger of the left hand and the other three fingers are spread fan wise on the abdomen. This allows the hand, needle and liver to move together freely with respiration and eliminates the necessity of the patient holding his breath. The remainder of the procedure is as in the adult. All patients are observed for signs of peritoneal bleeding for at least 6 hours after the procedure.

Precautions

Generally liver biopsy is only performed when the liver edge can be palpated. On special occasions, however, by introducing the needle at an acute angle, biopsies of impalpable livers can be obtained.

Any evidence of abnormal bleeding tendencies is considered a definite contraindication to biopsy. Generally the bleeding, clotting and prothrombin times are determined and only if all are within the normal range, is the biopsy done. A prothrombin time of 70 per cent or more is considered adequate.

Fever *per se* is not a contraindication but evidence of disseminated bacterial infection is. Viral and parasitic infections are not contraindications and indeed it is in the diagnosis of such infections that the biopsy is often especially valuable.

The Effects of Biopsy

There have been no fatalities nor any serious complications in any of these thousand patients. There were no instances of either excessive peritoneal bleeding, bile peritonitis or bile fistulas. In no patient was there evidence that the biopsy had caused any intensification or spread of his preexisting disease.

The older patients were questioned about the sensations. Aside from apprehension and the infiltration of the skin by local anesthetic, all with one exception, agreed that the procedure was completely painless.

On several occasions biopsy was performed on patients who had laparotomies for other reasons and with the liver in direct view. Biopsy is accompanied by about 5 ml. of bleeding in most instances, following the removal of the needle. In many patients, the opportunity presented itself to examine the liver at varying periods after biopsy, either at surgery or at autopsy. After 24 hours the biopsy site cannot be identified grossly.

The absence of complications of bleeding sometimes was surprising, for in some patients marked quantities of blood gushed from the needle. It is known,

however, that blood is rapidly absorbed from the peritoneum in infancy (prior to the refinement of transfusion technics the peritoneum was often the route of choice in administering blood to small babies) and it seems likely that even in instances in which bleeding has occurred, the blood is reabsorbed rapidly enough to prevent signs of blood loss.

The predominance of very young infants in this group of patients reflects the nature of the commonest problems encountered in pediatrics among the diseases of the liver. Jaundice in the immediate neonatal period is so common – approximately 25 per cent of all infants having some degree of physiologic icterus – that biopsy is rarely indicated in the first week of life. Jaundice persisting beyond the first week in full term infants is most often pathological. In recent years, because of the belief that in some diseases the earlier a definitive diagnosis is reached and treatment instituted, the less opportunity there is for

TABLE I

AGE OF PATIENTS AT TIME OF BIOPSY

0 – 1 wk.	7
1 – 3 wks.	271
3 – 6 wks.	223
7 – 12 wks.	206
3 – 6 mos.	81
7 – 12 mos.	63
1 – 2 yrs.	51
2 – 3 yrs.	18
4 – 6 yrs.	27
Over 6 yrs.	53
Total	1000

permanent liver damage to occur, biopsy has been performed as soon as it became apparent but the jaundice was indeed pathological.

The newborn infant's liver is almost always palpable 1-2 cm. below the costal margin and is always available for biopsy.

The relatively small number of patients over six months of age is explainable on several grounds. Primary liver diseases are relatively rare in childhood and by far the greatest number are related to congenital malformations. By six months of age the majority of patients with such anomalies have been sufficiently studied so that diagnosis has been established. Beyond this age the clinician feels relieved of the necessity of determining the existence of a genetically determined disease or of the possibility of a lethal malformation and jaundice, when it is seen in older children, is not viewed with the same alarm as it is in younger infants. Hence the desire for definitive diagnosis is somewhat lessened and biopsy is less frequently requested. That this attitude is not

justified or tenable needs little elaboration. The confusion existing at present in the published reports on the clinical nature of viral hepatitis in children need only be pointed out. This will be discussed further below.

The limited number of symptoms and signs constituting the reasons for biopsy indicate the difficulties presented by hepatic diseases in chlidren. Of all 1,000 patients, 732 were jaundiced and 667 had definite hepatomegaly. Only 122 patients in this series (12.2 per cent) had other complaints, and of these, 31 were biopsied for research purposes, and in 13 more, biopsy was a "last ditch" effort to arrive at a diagnosis.

In almost all patients a standard series of liver tests were performed. These included: blood bilirubin, direct and indirect, urine and fecal urobilinogen and bile, cephalin flocculation test, thymol turbidity test, prothrombin time,

TABLE II

INDICATIONS FOR BIOPSY

Jaundice*	211
Jaundice and hepatomegaly	521
Hepatomegaly (isolated)	75
Hepatomegaly in association with signs of generalized disease	71
Fever of unknown origin	16
Hepatic mass, localized	62
For diagnostic purposes	13
For scientific investigation	31
Total	1000

*The liver is normally palpable during the first year of life and the determination of whether it is or is not enlarged, is less exact than in adults. Probably many of these patients had some degree of hepatomegaly as well.

serum proteins, alkaline phosphatase and, in about 200 patients, serum transaminase. It was found impossible to correlate the results of these tests with the clinical manifestations of disease. Even the van den Bergh proved to be more variable in children than it is in the adult. Some children with intense icterus were found to have relatively low levels of serum bilirubin, i.e., in the neighborhood of 5 mg. per cent, whereas children with apparent but not intense icterus were sometimes found to have levels as high as 20 mg. per cent. Retrospectively, an attempt was made to correlate the results of the clinical laboratory tests with the diagnosis arrived at by biopsy studies. This too proved to be fruitless.

Although the list of diagnoses is long, the predominance of congenital malformations of the biliary system is striking and justifies the overpowering concern of pediatricians for this condition.

The relatively small number of cases of viral hepatitis cannot be taken as any indication of the frequency of this disease in childhood. It has been our observation that older children with a mild febrile illness accompanied by slight

TABLE III

DIAGNOSES ARRIVED AT BY BIOPSY

Congenital malformations of the bile ducts*	331
Giant cell formation of the liver ("neonatal hepatitis")*	53
Bile stasis, cause undetermined	87
Cirrhosis, cause unknown	43
Fibrosis, cause unknown	51
Viral hepatitis	40
Glycogen storage disease	12
Veno-occlusive disease of the liver (Budd-Chiari Syndrome)	2
Visceral *larva migrans*	21
Schistosomiasis	41
Pericholangitis, cause undetermined	7
Galactosemia	18
Letterer-Siwe's disease	1
Gaucher's disease	4
Niemann-Pick disease	2
Reticuloendothelial disease of unknown type	7
Lipogranulomatosis	1
Salivary gland virus infection (cytomegalic inclusion disease)	7
Herpes simplex, generalized (of newborn)	2
Neuroblastoma	18
Hepatoma	13
Liver cell type (12)	
Bile duct cell type (1)	
Congenital cystic disease of the liver	9
Extramedullary hematopoiesis	27
Sickle cell anemia	4
Leukemia	1
Histoplasmosis	2
Toxic hepatitis (known contact with poison)	12
Fatty infiltration	17
Accessory lobe of the liver	5
Congenital syphilis	2
Unclassified anatomic abnormalities, type and cause unknown	17
No anatomic evidence of disease	140

*Many of these patients had multiple biopsies. They have been counted as individuals for each biopsy in all tabulations.

jaundice are almost invariably classified as having "hepatitis" and only rarely is an attempt made to determine the exact nature of the child's illness. In fact, about half of the patients with viral hepatitis were biopsied at our own request

and urging. This was done to obtain material for another study which we were conducting at the time.

Disturbingly prominent, and therefore intensely interesting, are the categories of "no anatomic evidence of disease" and "unclassified anatomic abnormalities, type and cause unknown". The first group is composed predominantly of children who had hepatomegaly without other signs of disease. The clinical syndromes these patients presented were extremely varied and had in common only easily perceptible rapid enlargement of the liver. One small group of 4 patients were of special interest for they presented identical clinical signs. These 4 infants, all about 2 years of age, had a sudden onset of hemiparesis and hepatomegaly. The biopsies revealed no cause for the hepatomegaly and no diagnosis was ever arrived at in any of these patients. All recovered completely in about one month and had no sequela.

The patients with anatomic abnormalities of the liver all had clinical signs of liver disease, and in most the outstanding complaint was persistent severe jaundice. The variety of anatomic abnormalities of the liver appears to be almost infinite. Of this group we can only be certain that the appearance of the liver is unlike that seen in any of the recognized diseases. Explanation must await further experience. That these conditions represent earlier stages than are usually seen in the course of some recognized diseases seems a possibility. To the numbers of patients in whom either no disease or unclassifiable disease was found should, in all honesty, be added those in whom the conditions of cirrhosis, fibrosis, extramedullary hematopoiesis and bile stasis were diagnosed. Although these are anatomic lesions, in almost all instances they were the result of pathologic processes of which we have no understanding, and to achieve satisfaction from the recognition of a pathologic entity without knowledge of its pathogenesis is delusion. Altogether the patients with clinical evidence of hepatic disease whose condition could not be completely explained on anatomic bases numbered 365 (36.5 per cent of the total). In a sense it is humiliating to realize that to fully one-third of the children with evidence of liver disease, medicine can extend neither aid nor offer an explanation of their illness. This value, however, especially when considered in comparison to the quite different state of affairs in the hepatic diseases of adults, clearly indicates that the field of hepatic function and disease in children is one which requires study and because it is unexplored, one in which the hope for positive results is most promising.

The definitive diagnoses achieved by biopsy require little comment. It is desirable, however, to indicate, for the sake of emphasis, the almost absolute reliance which can be placed upon diagnosis by needle biopsy, especially in the acute problems of early infancy. Of the 278 patients (331 biopsies) with congenital malformations of the bile ducts, the diagnosis was later proven either at autopsy or surgery in 277. In only one patient was the diagnosis arrived at by

biopsy in error. This newborn infant was severely jaundiced for several weeks after birth. The biopsy was interpreted as congenital biliary atresia. Suddenly, however, at the age of two months, bile appeared in her stools and the jaundice cleared. Biopsy was again performed and still showed all the anatomic features of congenital biliary atresia. The patient remained well thereafter until she was lost to follow-up about a year later. No explanation for this could be found, other than the inferences derived from a single case report of a patient who had atresia of the biliary system in only parts of the liver[9].

A description of the histologic characteristics of congenital biliary atresia and the differences between the operable and the nonoperable varieties are given in another paper[10].

Giant cell transformation of the liver[11,12] remains somewhat of an enigma. Needle biopsy, however, has aided vastly in understanding the course the disease follows even if its causes have not been discovered. It is now known that the disease may progress along 4 possible lines; it may be immediately fatal in 10 per cent, in 15 per cent of the patients it remains static and proves fatal by about 2 years of age; in about 40 per cent of the patients, the disease clears, the liver returns to normal and there are no clinical or anatomic sequela; in 35 per cent of the patients, the hepatic cells return to normal but fibrosis, and eventually cirrhosis, results. Cirrhosis is always preceded by fibrosis in these patients and rarely is clearly established before the age of 5, although in a few patients it was evident by the age of 3 years. Three needle biopsies within the first year of life, one in the neonatal period, one at 3 months and one at 9 months allow a definite opinion to be formed as to which course the disease will follow.

The relatively large number of cases of schistosomiasis is misleading and deserves explanation. A definite effort to obtain these specimens from among the Puerto Rican population of New York City was made. It is of interest to note that this figure (41 patients), represents 68 per cent of the children biopsied, all of whom were known to have schistosomiasis and had large livers.

Especially gratifying were the diagnoses in the patients with salivary gland virus infection, herpes simplex infection and histoplasmosis, for these conditions had been suspected clinically and numerous other diagnostic procedures had been employed but had failed to provide proof of their existence.

Histologic examination of the liver in various states of malnutrition has proved of value in determining the efficacy of various forms of therapy and rather incidentally, for these patients are indicated on the chart as "for scientific study", gave interesting data on the rate and pathogenesis of fatty infiltration of the liver. It was noted that fat was visible at the periphery of the hepatic lobules after as short a period as 24 hours of starvation and that extensive fatty infiltration could occur in as short a period as 3 days. The rate of disappear-

ance of fat after the establishment of normal diet is apparently much slower, taking several weeks. These observations are very similar to those made in studies of kwashiorkor in which needle biopsy of the liver has been utilized extensively[13,14].

Comment

The avenues open to the pediatrician in the diagnosis and treatment of liver disease are extremely limited. As has been mentioned, the standard liver function tests are of relatively little value in children and thus ultimately most often the problem resolves itself into either biopsying or not biopsying. The only alternative to needle biopsy is a surgical procedure. This is undesirable for several reasons. First the small, sick infant is a poor surgical risk. Secondly, the biopsy obtained surgically is always from the superficial part of the liver and, in young infants this area is not representative of the liver as a whole for it is still undergoing development. Finally the surgical manipulation introduces artefacts which can be confusing to the pathologist[15].

The alternative to biopsy is clinical observation over a period of time. This is objectionable because irreversible liver damage may occur in children with surgically correctible lesions and may in themselves eventually prove fatal even after the basic defect has been repaired. No harm is done in observing those children whose disease heals spontaneously and they are the majority, but because confirmation of the diagnosis arrived at on clinical grounds cannot be obtained, the diagnosis is always open to doubt, and the prognosis must always be slightly guarded.

Especially in the small infant, definitive diagnosis is important for another reason. Parents often have questions about the advisability of having additional children because of the possible genetic basis of the patient's disease.

It is believed germane to mention the economic advantages of needle biopsy. Laboratory charges for a standard diagnostic investigation of hepatic function usually are about $125.00. To this must be added hospital charges and, as is most often the case in the obstructive lesions of early infancy, if surgical exploration and radiographic studies are performed, the total cost for diagnosis alone can well be many hundreds of dollars. The cost of needle biopsy is negligible comprising only the physician's fee and the cost of preparing the histologic section. In many instances it is not even necessary to admit the child to the hospital for the procedure. This economic detail is mentioned not for its own sake but because it so clearly illustrates the efficiency of biopsy as a diagnostic technic.

That clinical and laboratory studies are inadequate bases on which to establish diagnosis in hepatic disease in children is most clearly evident from the published reports of viral hepatitis in infancy and childhood[16-30]. After

reviewing a large number of these it has proved to be impossible to determine the clinical nature of the disease, for some reports indicate that the disease is most often a milder one than that seen in adults and is frequently subclinical. Other reports indicate that it is more severe than in adults and that the mortality rate can be as high as 40 per cent. There is a temptation to view the latter report as being more important, for anatomic confirmation of the diagnosis has been obtained at autopsy. Some variation is to be expected and is undoubtedly attributable to individual host factors and to the occurrence of different strains of viruses in different epidemics, but a more apparent explanation for the wide variations noted is found in the fact that the diagnosis of viral hepatitis in most instances is based solely on clinical grounds and only extremely rarely has it been confirmed by laboratory studies. In our own experience almost every patient over the age of 6 months referred to us because of jaundice has borne the diagnosis of "possible hepatitis". In fact, in this group of older children almost all the diseases listed under the conditions diagnosed occurred at least once. An almost unbelievable example was provided by a 4-year old boy who had been jaundiced for a "long time" but was not otherwise sufficiently ill for his parents to seek medical assistance. It was found that he had complete absence of the bile ducts. He lived until the age of 9 years.

Until that time when additional and better clinical tools are available for the study of hepatic disease in infancy and children, diagnosis must of necessity rest upon histologic examination of the liver. Beyond this, however, because of the ease of performance of biopsy, its innocuousness and low cost, it is an excellent research tool. At present this has been exploited in only a few investigations of diseases primarily of the liver. Its theoretical uses in the studies of nutritional problems, diseases of the reticuloendothelial system, the effects of chemotherapeutic agents on tumors metastatic to the liver and for epidemiologic studies, has not been attempted.

Conclusion and Summary

The use of needle biopsy of the liver as a diagnostic technic has proven to be effective in establishing a diagnosis and is safe and inexpensive. This is in sharp contrast to the results obtained by laboratory and clinical studies by the means of which many of the diseases of the liver in childhood are indistinguishable.

In this group of patients 27 distinct disease entities were found, 5 categories of anatomic diagnoses were encountered, i.e., cirrhosis, but the etiology and pathogenesis of the diseases leading to the changes were not determined. In 14 per cent of all patients with signs of liver disease, no anatomic lesion of the liver could be found.

Needle biopsy of the liver proved especially valuable in the diagnosis of congenital malformations of the biliary system in very early infancy, and proved

a reliable guide in the differentiation of the operable from the inoperable varieties of these malformations. Of the more than 250 patients with congenital biliary atresia who were biopsied, an error in diagnosis was made in only one.

It was found that in about one-third of all patients with signs and symptoms of liver disease in infancy or early childhood, current knowledge and technics are inadequate to determine the nature of the illness. Although needle biopsy cannot be expected to be a source of additional information in all of these, for in approximately half there are no anatomic counterparts to the physiologic disease, in the remainder lesions are produced and it is only because some of them have been so recently discovered that so little is known of them.

Finally the feasibility of needle biopsy of the liver as a research tool and as a means of studying diseases of children other than those of the liver is suggested.

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THE ROLE OF SURGERY IN THE TREATMENT OF PORTAL HYPERTENSION*†

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At present there is considerable confusion regarding the place of surgery in the treatment of portal hypertension. Initially there was general acceptance of the recommendation of Whipple[1] and Blakemore and Lord[2] to decompress the portal venous bed by portacaval shunt to prevent recurrent bleeding from esophageal varices. Cohen[3], Ripstein[4], and Nachlas[5] have challenged the validity of this concept and they question whether portacaval shunting procedures are ever indicated.

There is likewise disagreement as to the preferred treatment of the patient who is acutely and massively bleeding from esophageal varices. None would deny the value of the Sengstaken tube in preventing some patients from exsanguinating. There are those (Linton[6], Welch[7], and Crile[8]) who advise emergency operation after bleeding has been temporarily controlled with the tamponading bag, while others strongly advise against it. If operative intervention is deemed necessary, there are enthusiastic advocates for ligation of the bleeding varices by the transabdominal route[7], or the transthoracic route[6,8], or for performing an emergency portacaval shunt[9].

Although in the past intractable ascites has been considered a relative if not absolute contraindication to venous shunt surgery, recently interest has been aroused in the feasibility of decompressing the liver by means of a "double-barreled" portacaval shunt. Functionally this is similar to a side-to-side portacaval shunt.

It is the purpose of this report to present our current method of management of patients with portal hypertension who are:

1. chronically bleeding from esophageal varices
2. acutely and massively bleeding from esophageal varices
3. having intractable ascites

Chronic Recurrent Bleeding From Esophageal Varices

It is generally accepted that esophageal varices develop in response to abnormal elevations in portal venous pressure as a result of either an intra-

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hepatic or extrahepatic blockage. Portal hypertension and bleeding varices due to portal venous thrombosis (extrahepatic block) is primarily a disease of children and young adults whose liver function is not severely impaired. These young patients are good surgical risks and one major hemorrhage in our opinion is ample indication for surgery. We prefer a transthoracic ligation of varices in the infants and small children and a splenorenal shunt in the young adults and older patients in this group for reasons which will be subsequently mentioned in the discussion of the acute, massive bleeders.

In distinct contrast to the above group of patients are those with portal hypertension and recurrent bleeding esophageal varices secondary to an intrahepatic block from some form of cirrhosis. Almost without exception these patients are much poorer surgical risks because of their underlying liver disease. For this reason, even though the incidence of recurrent bleeding is extremely high, it is with some reluctance that operation is recommended in many of these patients.

The crux of the matter would seem to be whether: 1. adequate portacaval shunt will prevent bleeding from esophageal varices and, 2. does prevention of further bleeding materially improve the life expectancy.

There is available today a considerable experience with shunting operations. Almost without exception the observation has been made that an adequate shunt between the portal and systemic venous systems will significantly lower the portal venous pressure and give the patient a high degree of protection from future hemorrhage. A series reported by Child[10] is quite typical of our experience and that of others. In this group, 115 gastrointestinal hemorrhages occurred in 56 patients before portacaval shunt, and in the 48 patients who survived operation followed one month to four years, there were no further hemorrhages. Admittedly this protection is not always 100 per cent, nor would such be expected since bleeding from an esophageal varix is probably not solely the result of mechanical rupture. Wangensteen[11] has focused attention upon the contributory role of peptic esophagitis. Hepatic failure itself, with diminished capacity for tissue repair and defective blood clotting mechanism, is certainly important in some cases. To challenge the efficacy of a portacaval shunt in preventing hemorrhage from esophageal varices by citing the occasional exceptional case seems, however, unwarranted.

A more difficult question to answer, with valid statistical data at least, is whether a successful shunt procedure improves the patient's life expectancy. Previously published survival curves comparing operative and nonoperative groups of patients have been justifiably criticized[3,5]. Although it is true that 60 to 70 per cent of patients bleeding from esophageal varices who are treated nonoperatively will be dead in one year following the initial hemorrhage, it is equally true that many, if not most, of these patients, because of the severity of their liver disease, were never surgical candidates. To compare the survival

curves of a random group of bleeding cirrhotics with the highly selected group of operative patients obviously has led to unjustified enthusiasm for the shunting procedures. A more valid appraisal of this problem should be forthcoming from certain institutions who, because of their conviction that the shunt operations are of questionable value in this disease, are now doing a controlled study to eliminate the factor of case selection. Palmer, however, reported a reasonably controlled series of 105 patients for whom operation was recommended[12]. Approximately 50 per cent of these patients refused operation while the remainder had a portacaval shunt. Of those 48 patients who refused operation and were treated medically, 19 died in one year as a direct result of recurrent bleeding from esophageal varices. In the operative group, the surgical mortality was 10

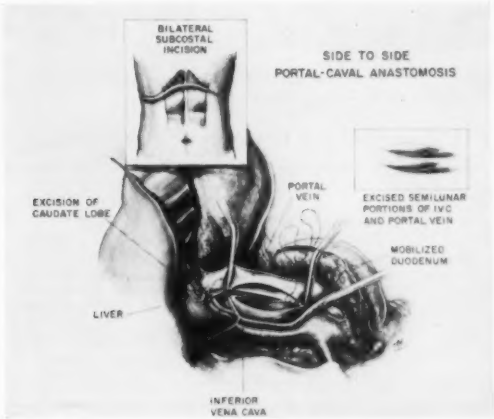


Fig. 1—Technic of side-to-side portacaval anastomosis. Semilunar segments of the portal vein and inferior vena cava are excised. A wedge-shaped segment of the caudate lobe is excised, if necessary, for adequate approximation of portal vein and inferior vena cava. (Courtesy of *Annals of Surgery*[13]).

per cent and none of the patients subsequently died as a result of recurrent bleeding. Nevertheless, there is no doubt that liver failure is aggravated by surgery. It is likewise quite probable that any effective shunting procedure diverts a significant amount of blood away from the liver, which may tend to depress liver function still further.

On the other hand, it is well recognized that hemorrhage itself materially injures the liver. It is not infrequent that a patient whose liver disease is in a state of static compensation, progressively deteriorates with each of a succession of hemorrhages and finally dies of hepatic failure. The course, however, of hepatic cirrhosis is so capricious and hepatic damage is so difficult to quantitate that it becomes a very complicated matter to decide whether operation has or has not improved the prognosis in certain of these patients.

We join those who feel that portacaval shunt does dramatically reduce the incidence of recurrent bleeding from esophageal varices, and does significantly increase the life expectancy of these patients.

Indications and preparation of patients for operation:—One major hemorrhage, in our opinion, qualifies a patient as a potential surgical candidate. Operation is temporarily deferred in some instances because of borderline hepatic reserve. Several criteria have been used to guide the selection of operative candidates:

1. How good was the patient's appetite, and could he eat a reasonably high protein diet without clouding of consciousness?

2. More than a trace of jaundice, *fetor hepaticus*, or any systemic bleeding diathesis were strong contraindications to surgery.

TABLE I

OPERATIONS FOR INTRAHEPATIC OBSTRUCTION

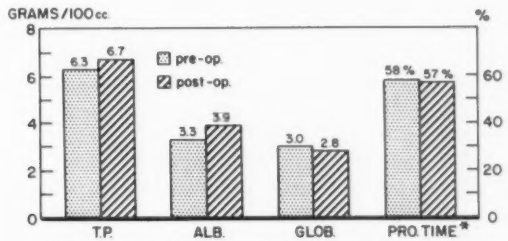
	Indications for operation	Etiology		Results
Procedure	Bleeding varices	Alcoholic cirrhosis	Hepatitis	Excellent
S-S (18)	17*	13	5	18† (2 mos., 5.5 yrs.)
E-S (1)	1	1	0	1 (7 mos.)
S-R (1)	1	0	1	1 (5.5 yrs.)

*One additional S-S shunt for ascites.
†3 late deaths from hepatic failure.
Courtesy of *Annals of Surgery*[13].

3. Marked depression of the serum albumin, indicating impaired ability of the liver to synthesize protein, was a poor prognostic sign. Nevertheless, neither a low serum albumin nor any of the other relative contraindications did, of itself, automatically cause the patient's rejection. Each case was weighed on the basis of the total picture.

Every effort is made to get the patient in the best preoperative condition possible. A diet, adequate in calories and high in both protein and vitamins, is maintained as long as practical. The degree of abnormal water retention controls the amount of sodium chloride allowed in the diet. If the patient requires surgery before an adequate hematocrit, blood volume, and serum albumin concentration can be achieved with diet and iron therapy, blood transfusions and, sometimes, infusions of salt-free human albumin are given. Vitamin K is routinely administered for reduced prothrombin concentration.

Operative technic:—With the patient in the supine position, a generous bilateral subcostal incision is made extending laterally around the right costal margin (Fig. 1). The hepatoduodenal ligament is exposed, the hepatic artery identified, and the common duct mobilized and gently retracted out of the way. The second portion of the duodenum is Kocherized, mobilizing it and the head of the pancreas to expose the portal vein which is freed from the head of the pancreas to its bifurcation in the liver hilum. The inferior vena cava is cleared on its anterior surface but not completely mobilized. Occasionally a V-shaped wedge of the enlarged caudate lobe will have to be excised to allow adequate exposure. The portal vein is then occluded proximally and distally with non-crushing vascular clamps. The inferior vena cava is partially occluded with a Satinsky clamp. An elliptical segment is excised from each vessel at the site of the proposed anastomosis; this will prevent subsequent closure which otherwise may occasionally occur with the use of linear incisions in the vessels. The two



*Preoperative values indicate the best level that could be achieved with treatment. This is compared with post-operative values with patients on no specific therapy.

Fig. 2—Preoperative and postoperative studies (average values) of hepatic function in nine unselected cases (Courtesy of *Annals of Surgery*[13]).

veins are then approximated with a continuous suture of No. 0000 silk, interrupted in two places with stay sutures to prevent a "purse-string" effect. The diameter of the anastomosis is made slightly larger than the diameter of the portal vein. Portal venous pressure is measured immediately before and after construction of the shunt. A splenectomy is not routinely done unless there is tremendous enlargement of the spleen with evidence of hypersplenism.

Results:—In a previous report[13] our experience with 19 cases of portacaval shunt for bleeding esophageal varices was presented (Table I). Since then, four additional patients have been operated upon with no operative mortality. There have been three late deaths from liver failure. One patient had moderately severe upper gastrointestinal tract bleeding several months postoperatively, but was shown to have an active duodenal ulcer which responded promptly to medical management. Two patients showed neurological symptoms postoperatively similar to those described by McDermott[14], Sherlock[15], and Hallenbeck[16], and details of their course and management were previously discussed. No such

syndrome has appeared in the subsequent four patients. Hepatic function studies in nine unselected patients who had portacaval shunts for esophageal varices four months to five years previously, revealed a slight but definite increase in the total protein and serum albumin levels (Fig. 2). The average of the prothrombin times was unchanged. The preoperative value, however, represented the best level that could be otained under intensive treatment, while the postoperative value was determined during a period when the patients were under no specific therapy. This data in conjunction with our clinical impressions would suggest that these patients had been protected from recurrent bleeding, and that a side-to-side portacaval shunt did not further depress liver function. It seems logical to assume that the life expectancy of these patients has been increased. The rate of progression of the cirrhotic process is, of course, the major prognostic factor in these patients. Continued alcoholic intake and inadequate diet will further deplete the hepatic reserve and negate any beneficial effects achieved by a shunt procedure.

Acute Massive Bleeders

Sudden, massive hemorrhage from esophageal varices may be a life-threatening catastrophe, and the treatment of such a patient will tax the skill of both the internist and surgeon.

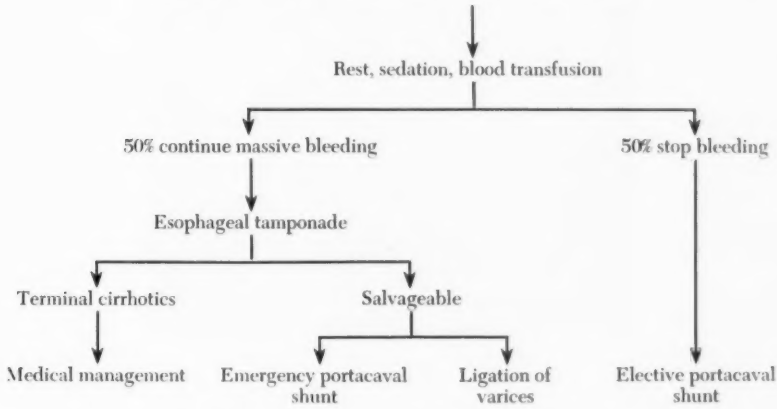
To establish with reasonable certainty the site of bleeding may in itself be difficult, for in some individuals the first hemorrhage announces the presence of hepatic disease and secondary portal hypertension. In the known cirrhotic (or in patients suspected of having Banti's syndrome), such a bleeding episode comes as no particular surprise. As Welch[7] and others have pointed out, however, there is an increased incidence of peptic ulcer in patients with cirrhosis, so that this possibility as a source of the hemorrhage as well as others must not be ignored. If the patient is not known to have cirrhosis and by history or physical examination one cannot establish this diagnosis, we have relied primarily on the bromsulfalein excretion test to screen these suspects. If the bromsulfalein retention exceeds 15 per cent in 45 minutes, one can be reasonably sure that significant liver disease is present to justify the presumption that the site of the bleeding is esophageal varices. An esophagram in the massively bleeding patient is impracticable as well as hazardous, but should be obtained if bleeding ceases to confirm the diagnosis. If it is necessary to resort to the use of a Sengstaken tube to prevent exsanguination, the prompt cessation of bleeding following esophagogastric tamponade establishes beyond a doubt the source of the hemorrhage.

It has been the general observation that if patients hemorrhaging from esophageal varices are treated promptly and effectively by rest, sedation and blood replacement, 50 per cent of this group will promptly stop bleeding (Table II). Any patient, however, who has bled massively because of esophageal

varices is very likely to do so again. Such hemorrhages are not only hazardous in the sense that any major hemorrhage is risky, but, in addition, each hemorrhage is an added insult to the diseased liver. As McDermott[14], Welch[7], and others have pointed out, large "forced feedings" of blood such as occur with repetitive bleeding episodes result in a markedly elevated blood ammonia and probably other noxious breakdown products which the diseased liver cannot clear. Thus, hepatic coma is frequently precipitated by gastrointestinal bleeding, and repeated hemorrhages promote progressive hepatic deterioration. For these reasons, any patient in whom portal hypertension has led to bleeding is considered a candidate for a side-to-side portacaval shunt, although some candidates are rejected, at least temporarily, because of signs of questionable liver reserve necessary to survive the catabolic shock and stress of a major operation.

TABLE II

ACUTE, MASSIVE BLEEDING FROM ESOPHAGEAL VARICES



Intensive efforts are made to ready the patient for surgery as discussed in the preceding section. If possible, operation is performed in two to three weeks or whenever the patient's condition is felt to be optimal. Undue procrastination in the hope of obtaining further improvement is fraught with the hazard of recurrent bleeding and the loss of hard earned ground.

The remaining 50 per cent of the massively bleeding patients will continue to bleed, and esophageal tamponade with the Sengstaken tube should be employed promptly and may be life-saving. Its use is not without occasional complications such as violent uncontrollable retching, and ulceration or pressure necrosis at the gastroesophageal junction. Consequently, some discretion should be employed in its use, although concern for these potential hazards, of course, does not justify jeopardizing the patient's life. Of the persistent bleeders, an

appreciable number will be advanced cirrhotics for whom the hemorrhage is the *coup de grace* terminating a steady downhill course of progressive hepatic deterioration. Medical treatment including the prolonged use of a tamponading bag, if necessary, must be relied upon for none of these patients are candidates for any operative procedure. Regardless of the treatment instituted, most of these patients will not survive.

Once resorting to the Sengstaken tube to control bleeding, we would agree with Welch that little is to be gained by repeated trial at deflating the bag in the hope that bleeding will stop. Rather, he recommends a prompt emergency ligation of varices with the inflated bag in place[7]. Linton[6], Hallenbeck[16], and Crile[8] likewise advocate a direct attack upon the bleeding site, although this procedure is generally recognized as a temporizing measure to be followed in a

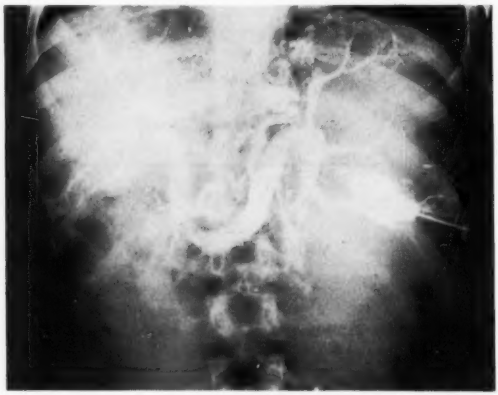


Fig. 3—Splenoportogram obtained on the operating table in patient suspected of having an extrahepatic portal block. The demonstration of a normal portal vein excluded this diagnosis and a side-to-side portacaval shunt was constructed.

few weeks by a definitive portal-systemic shunt. In one series reported by Linton, 36 per cent of the patients had recurrent bleeding within two weeks to five months while awaiting shunt surgery after having their varices ligated as an emergency procedure. Crile, admittedly referring primarily to patients with bleeding varices secondary to extrahepatic block, states that variceal ligation is as definitive as hemorrhoidectomy and that no future bleeding need be anticipated. The literature does not bear out such a tenet for bleeding varices in general, although the outlook for the patient with extrahepatic block is considerably more favorable than for those patients with intrahepatic block as far as future bleeding is concerned.

It obviously would be most desirable to subject these precariously ill patients to only one definitive procedure rather than two. For this reason, we agree

with Child[10] and O'Sullivan[9] that an emergency portacaval shunt with the Sengstaken tube in place is the treatment of choice for operative candidates. The criticism leveled at this procedure under these circumstances is that it is too big an operation, that it cannot be relied upon to stop the acute bleeding, and that construction of a shunt may divert a critical amount of portal blood flow from the liver. It has been our impression that a ligation of varices especially by the transthoracic route is not such a simple and expedient procedure. The mortality rate varies from 15 to 50 per cent depending a great deal on case

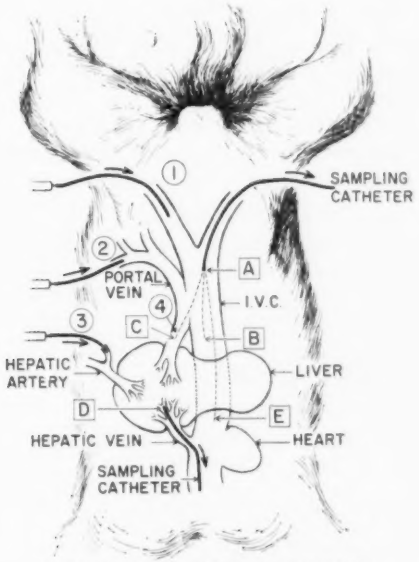


Fig. 4—Technic used to obtain liver flow and function studies following construction of side-to-side portacaval shunt in dogs. Sampling catheters are placed in the hepatic vein, central portal vein, and inferior vena cava, and injection catheters in the hepatic artery, femoral vein, and peripheral portal vein.

selection. If then one admits the necessity of having to do a subsequent portacaval shunt with its current mortality of 10 to 20 per cent, the combined mortality is certainly as high or higher than that reported for the emergency portacaval shunt, even though statistics are limited as yet for the latter procedure. It would appear that acute bleeding will be controlled by such an attack, if an effective shunt is constructed and the tamponading bag is left inflated for 24 hours postoperatively and then removed[9]. Undoubtedly, diversion of some portal blood away from the liver at a time when the liver is being

challenged by a severe hemorrhage may be detrimental. How critical this may be is not known. Because side-to-side shunts leave a potential portal pathway to the liver, as well as effectively decompress the portal bed, we feel this is an added reason for doing a side-to-side rather than an end-to-side shunt.

It is our recommendation then, that having controlled the hemorrhage with the Sengstaken tube, blood volume should be restored ideally with fresh blood, clotting deficiencies corrected, the bowel evacuated of blood as effectively as possible by means of enemas and occasionally cathartics, and the patient taken to surgery for a side-to-side portacaval shunt usually within 36 to 48 hours from the onset of the hemorrhage. During this brief preoperative period those patients with borderline liver reserve may show signs of frank decompensation contraindicating any operative procedure. Stabilization and beginning improvement can be anticipated in the remaining patients provided the tamponading bag is not released and the patient is protected from another hemorrhage. Our expe-

TABLE III

DIFFERENTIAL LIVER FLOW AND FUNCTION FOLLOWING SIDE-TO-SIDE PORTACAVAL SHUNT

	Flow (ml./min.) (Dye)	BSP		O_2 Sat.	
		Flow (ml./min.)	mg. %	Vol. %	% Sat.
PV	368	506	3.78	13.26	73.8
HV	149	134	1.78	6.36	35.4
HA	—	—	4.42	16.37	91.7

PV = portal vein, HV = hepatic vein, HA = hepatic artery.

rience with the above plan of management has been limited, but on the basis of the favorable results in these few patients and the observations of others[9] we feel it is the most rational plan of therapy.

In infants and children with an extrahepatic block, a transthoracic ligation of the bleeding varices is performed. A subsequent splenorenal shunt may be necessary if the patient has recurrent bleeding. The incidence of recurrent hemorrhage, however, is much less in this group than in patients suffering from cirrhosis, and a shunt operation may never be necessary. Percutaneous splenoportograms are obtained in the operating room on those patients in the young adult or older age groups in whom there is considerable doubt as to the site of portal venous obstruction. In these patients a splenorenal shunt is performed if an extrahepatic block is demonstrated. If a normal portal vein can be visualized (Fig. 3), a portacaval shunt is performed. Our policy has been to follow the young patients, with an extrahepatic block, who have had their

varices ligated to see if they bleed repetitively, in which event a splenorenal shunt is performed. This seems a justifiable course of action since in contrast to the typical patient with cirrhosis, liver function is usually relatively normal, the patient is young and better able to tolerate a bleeding episode, and the additional time gained may be several years. This is extremely critical where a young child is concerned, for vascular anastomoses, especially venous anastomoses between small vessels, are technically difficult and prone to thrombose. A shunt procedure in the infants and young children is therefore deferred indefinitely, or until the patient demonstrates by recurrent bleeding episodes that further conservative management has little hope for success and indeed may jeopardize the patient's life.

Intractable Ascites

In the past we have felt that patients with intractable ascites were not helped by any form of portacaval shunt. This opinion was based on several unsatisfactory results early in our experience. In retrospect these critically ill patients by current standards were not suitable operative candidates. For although there is still no unanimity of opinion in regard to the pathogenesis of ascites, it is common knowledge that far advanced cirrhosis frequently is accompanied by ascites. The presumption has been that this is an indication of marked hepatic decompensation, and in many patients certainly this is true. There are, however, a significant number of patients with intractable ascites in whom liver function appears to be only moderately impaired. Evidence is accruing to suggest that ascites in cirrhosis is due to intrahepatic venous hypertension rather than to splanchnic venous hypertension. In those patients with an acute exacerbation of their cirrhosis with ascites, the hepatic venous obstruction is believed related to a diffuse intrahepatic cellular edema secondary to both protein and electrolyte imbalances. Proper diet and medication reverses this process and the congestive hepatomegaly and ascites disappear. In patients with chronic intractable ascites, the obstruction to hepatic venous outflow is related to scarring and obliteration of much of this vascular bed. Numerous observations would strongly support this hypothesis: 1. portal hypertension *per se* is seldom accompanied by ascites; 2. injection and histological studies by Madden[17] have shown that where the cirrhotic obstruction to hepatic blood flow resides predominantly in the hepatic venous outflow tracts, massive ascites is prominent; 3. Budd-Chiari's syndrome (primary hepatic venous thrombosis) is invariably accompanied by severe ascites. There is also evidence to suggest that the source of the ascites is from the surface of the liver (Freeman[18], Mallet-Guy[19], Hyatt and Smith[20]). Although the actual route of the intrahepatic lymph flow has not been completely determined, available data support the theory that consequent to congestion of the liver, there is engorgement of the subcapsular lymphatics and the lymphatics of the *porta hepatis* with extravasation of lymph from these engorged lymphatics into the peritoneal cavity.

It would seem logical, therefore, that a reduction of intrahepatic venous pressure should be beneficial in these patients. Reinhoff[21] hoped to accomplish this by hepatic artery ligation, but this procedure has not been accepted because in many cirrhotic patients this vessel supplies the major if not entire hepatic blood flow. Welch[22] has recently called attention to the fact that nature has attempted to "decompress" the liver by the development of intrahepatic arterioportal anastomosis. Although these shunts (as well as arteriosinusoidal communications) are normally present, Herrick[23] showed in 1907 that in cirrhosis these arterioportal shunts are increased. In cirrhotic livers from patients with ascites, he demonstrated that portal pressure rose markedly as hepatic arterial pressure was increased, and that the volume of portal venous return flow was greater than that recovered from the hepatic veins. This is in marked contrast to hepatic artery perfusion studies in the normal liver where hepatic venous return flow is greater than portal venous return.

We agree with the proposal of Welch[22] that a side-to-side portacaval shunt not only will vent the hypertensive splanchnic venous bed, but will also provide a decompressive hepatic outflow tract for retrograde flow into the proximal limb of the portal vein. Thus, a portion of the hepatic artery blood can drain into the vena cava by way of the natural intrahepatic arterioportal and artificially created portacaval anastomoses. Recently McDermott[24] performed a "double-barreled" portacaval shunt to accomplish a similar hemodynamic result. In this procedure the portal vein is divided and each transected end is anastomosed individually end-to-side to the inferior vena cava. It would appear to us that the "double-barreled" and the side-to-side portacaval shunt should be functionally similar.

At operation we have demonstrated by radioisotope injection technic that in the cirrhotic patient there is very significant hepatic arterial reflux flow into the portal vein, and that this retrograde flow is markedly increased by lowering the portal venous pressure with a side-to-side portacaval shunt[13]. The criticism has very logically been raised that this may reflect a detrimental arteriovenous shunt, and that this is made even more deleterious by altering the hemodynamics so that such flow is increased.

In an effort to further elucidate this problem the following experimental technic was employed (Fig. 4). Side-to-side portacaval shunts were performed in normal dogs. Six weeks later a differential liver blood flow and function study was carried out. A sampling catheter was placed under fluoroscopy into the hepatic vein wedge position. A second sampling catheter was passed up the femoral vein into various positions in the inferior vena. This catheter was subsequently passed through the anastomosis well into the portal vein on the liver side of the shunt. Injection catheters were positioned in the femoral vein, an hepatic arterial branch, and a peripheral portal venous tributary. Simultaneous determinations of O_2 saturation, bromsulfalein clearance, and blood flow

(indocyanine green technic) were made in the hepatic artery, portal vein, and hepatic vein. These preliminary data are recorded in Table III, and the following observations can be made:

1. Dye injected into the distal portal vein 2 is completely recovered in the IVC at position B and none is recovered in the hepatic vein D indicating most if not all of the portal flow is through the shunt.

2. Dye injected into the proximal portal vein 4 and directed toward the liver is completely recovered in the IVC at position B, and none is recovered from the hepatic vein D, indicating reflux liver blood flow retrograde through the shunt.

3. Dye injected into the hepatic artery 3 is recovered in both the portal C and hepatic vein D indicating the presence of communications between the hepatic arterial and both hepatic venous beds.

4. The source of the large portal venous blood flow must be the hepatic artery because of the findings in 1. That this arteriovenous communication involves the sinusoidal bed, at least in part, can be inferred from the extraction of 0.64 mg. per cent BSP (4.42-3.78), and the utilization of 3.11 vol. per cent of oxygen (16.37-13.26).

As mentioned previously, these studies were in normal dogs, and we have insufficient data at present to confirm or deny such findings in the human with cirrhosis. These investigations are currently in progress and may add to our limited understanding of the altered hemodynamics in the patient with cirrhosis both before and after the side-to-side portacaval shunt.

Until such information is available to disprove its value, we recommend a side-to-side portacaval shunt for carefully selected patients with intractable ascites. Again, our personal experience has been limited, but we are encouraged by the clinical report of Welch[22]. Six patients with intractable ascites underwent side-to-side portacaval shunt with dramatic subsidence of their ascites, and showed improvement of liver function over a short follow-up period of two to eight months. The early results of McDermott using the "double-barreled" portacaval shunt have likewise been encouraging. Further clinical observations must be made before such procedures can be recommended without reservation.

Summary

1. The problem of recurrent bleeding esophageal varices secondary to portal hypertension is discussed.

2. The rationale for the emergency portacaval shunt operation in those patients with cirrhosis who are acutely and massively bleeding is presented.

3. Experimental liver flow and function studies suggest that a side-to-side portacaval shunt may be beneficial in patients with ascites as well as bleeding varices.

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EVALUATION OF PHOTOTURBIDIMETRIC TECHNICS FOR THE DETERMINATION OF SERUM AMYLASE, LIPASE AND ESTERASE*

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Serum enzyme determinations have proven of value in the diagnosis of a variety of disease states. In recent years there has been an increasing tendency to translate fundamental enzyme knowledge into clinical tools for the study of disease[1]. Several years ago in the course of a study of pancreatic physiology, phototurbidimetric methods for the determination of amylase, lipase and esterase in canine pancreatic juice were developed[2,3,4]. In comparison with standard analytic procedures, these had the advantage of simplicity and rapidity while still maintaining a high degree of specificity and accuracy. Only limited studies on the application of these methods to serum enzyme alterations in human

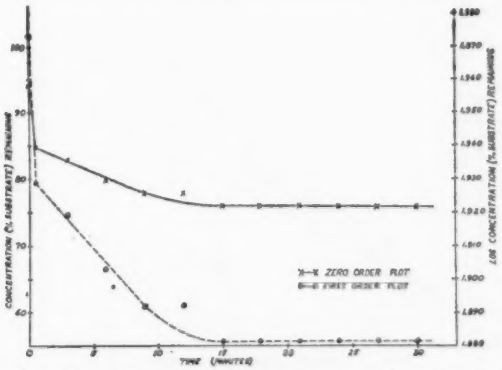

Fig. 1—Hydrolysis of starch substrate by serum amylase as a function of time. Zero and first order reaction plots.

disease states were performed[4]. It was the purpose of the present study to further investigate the clinical applicability of these methods.

METHODS

Amylase:—A modification of the phototurbidimetric method previously described[2] as *procedure III* was employed. In this procedure amylase activity is

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estimated from the decrease in optical density of a turbid starch solution produced by enzymatic hydrolysis. The initial starch substrate concentration was changed so that the turbidimetric reading would lie between 200 and 300 on the Klett-Summerson photoelectric colorimeter scale, within the portion of the scale which can be read most accurately[5]. The substrate contained 8.5 ml. of a commercially available standard starch suspension† plus 98 ml. of buffer-sodium chloride solution (4 parts phosphate buffer, pH 7.2, to 1.14 parts M/1 sodium chloride). The enzyme solution consisted of 0.2 ml. serum plus 0.3 ml. physiological saline in a test tube. After prewarming, this was added to 5 ml. of prewarmed substrate in a colorimeter tube by the previously described pouring technic. Incubation was then allowed to proceed for five minutes at 37° C.

Lipase:—A modification of the phototurbidimetric method previously reported[4] was employed. In this procedure lipase activity is estimated from the

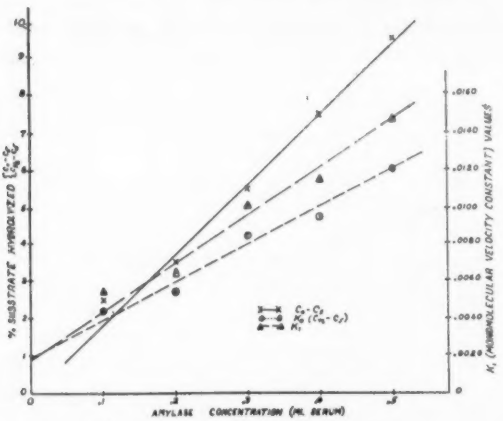

Fig. 2—Hydrolysis of starch substrate as a function of enzyme concentration. Comparison of methods of estimating serum amylase concentration.

decrease in optical density of a turbid fat emulsion produced by enzymatic hydrolysis. The substrate, pH 8.6, contained 4 ml. of 1.12 per cent fat emulsion (prepared from a commercially available vegetable oil emulsion* plus buffer), 0.4 ml. 1 per cent potassium oleate solution, 0.75 gm. sodium desoxycholate, and 3 gm. gelatin, made up to a final volume of 100 ml. with veronal buffer (pH 9.2). One tenth ml. serum was added to 5 ml. of prewarmed substrate in a colorimeter tube. Incubation was then allowed to proceed for 15 minutes at 37° C.

†Available from the Hartman-Leddon Co., Philadelphia, Pa.

*Lipo-Mul-Oral, a 40 per cent fat emulsion kindly supplied by the Upjohn Co., Kalamazoo, Mich.

Esterase:—The method employed to determine the esterolytic activity of serum was identical with that used for the determination of lipolytic activity except that in the substrate, tributyrin, 0.15 per cent, was substituted for the natural fat, and sodium desoxycholate was omitted[4]. The final substrate contained 0.15 ml. tributyrin, 0.4 ml. 1 per cent potassium oleate solution, and 3 gm. gelatin, made up to a final volume of 100 ml. with veronal buffer (pH 9.2). Because of the large size of the tributyrin globules, it was necessary to emulsify the tributyrin by blending the substrate in a Waring Blendor for five minutes. One tenth ml. serum was added to 5 ml. of prewarmed substrate in a colorimeter tube. Incubation was then allowed to proceed for 15 minutes at 37° C.

Incubation and colorimeter:—The incubation periods for each method have been described *(v.s.)*. Thirty seconds before the end of incubation the colorimeter tube was removed from the water bath, the outside wiped dry, the tube inverted once and then placed in the colorimeter. Timing of the beginning and end of incubation were each accurate to within ± 5 seconds.

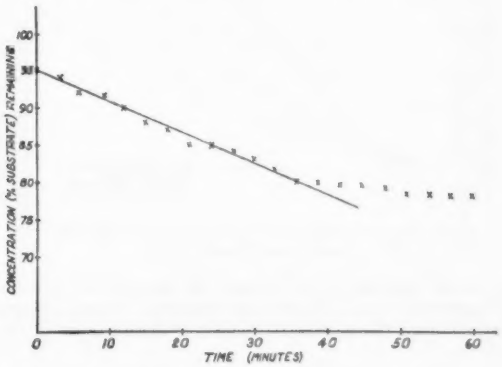

Fig. 3—Hydrolysis of fat substrate by serum lipase as a function of time.

The Klett-Summerson photoelectric colorimeter, using a number 66 filter (640-700λ) was employed throughout.

Substrate and serum blanks:—For each enzyme method one substrate blank, in which the serum is replaced by an equal volume of physiological saline, was included in every series of determinations. The substrate blanks for the amylase, lipase and esterase methods read 200 ± 10, 230 ± 10, and 265 ± 10 Klett scale units, respectively. Initial substrate concentrations were adjusted to lie within this range, as marked variations in substrate concentrations influence enzyme activity.

For each serum specimen analyzed, a serum blank, in which the substrate was replaced by an equal volume of buffer (a buffer-sodium chloride solution

for amylase determinations), was run. The Klett reading of the serum blank, which represents optical density due solely to serum color, was subtracted from the final Klett reading of the serum-substrate tube in order to obtain the Klett reading corresponding to the substrate concentration remaining.

Estimation of enzyme activities:—Calibration curves were made for each enzyme method as previously described[2,4] except that for the amylase method, 0.5 ml. physiological saline plus 5 ml. substrate was taken as 100 per cent starch concentration.

Activity was expressed directly as $C_o - C_t$ (initial substrate concentration minus substrate concentration remaining at the end of incubation), taking both readings from the substrate calibration curves for each of the respective methods.

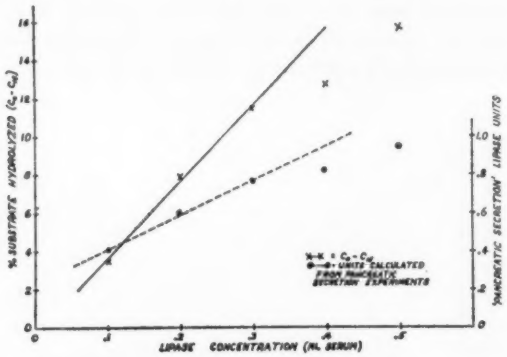

Fig. 4—Hydrolysis of fat substrate as a function of enzyme concentration. Comparison of methods of estimating serum lipase concentration. "Pancreatic secretion" lipase units were calculated from the equation: number of lipase units = (% digestion + 5.64) / 22.4 (ref. 4).

Enzyme Kinetics

Amylase time studies:—Results of a typical study designed to demonstrate the relationship between substrate hydrolysis and time of incubation is illustrated in Figure 1. Zero and first order reaction plots are presented. Three different components of the zero order curve are discernible, an initial period of very rapid hydrolysis during the first half minute, a period of less active hydrolysis for the next 8½ minutes during which there is a rectilinear relationship between degree of hydrolysis and time of incubation and, finally, a plateau period. The monomolecular plot resulted in a curve of very similar configuration. Thus from 1/2 to 9 minutes the course of the reaction agrees fairly closely with the concept of zero order and also with that of first order reaction. The reaction appears to be a complex one with no single concept of enzyme kinetics explaining the over all course.

Amylase concentration studies:—Hydrolysis of the substrate as a function of enzyme concentration was investigated in experiments in which various amounts of the same serum were employed. One such study is illustrated in Figure 2. Inasmuch as the time studies indicated close agreement with both zero and first order kinetics for the period from ½ to 9 minutes of incubation, the zero order (K_0) and first order (K_1) reaction constants calculated from the ½- and 5-minute concentration determinations are presented, as well as per cent digestion in five minutes ($C_0 - C_5$). A rectilinear regression on enzyme concentration (volume of serum) is noted with all three estimates of enzyme concentration. Although in this study the regression of per cent digestion in five minutes on volume of serum passes through the zero intercept, it did not do so in other studies, both the slope and the intercept of the regression varying with different serum specimens. Inasmuch as none of the three estimates demon-

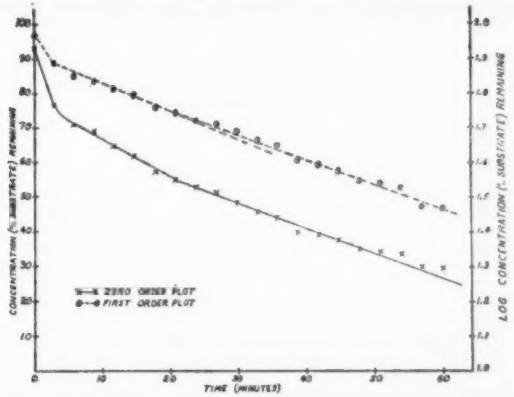

Fig. 5—Hydrolysis of tributyrin substrate by serum esterase as a function of time. Zero and first order reaction plots.

strated any superiority, per cent digestion in five minutes, the simplest from the technical point of view, was adopted as the measure of enzyme concentration. It must be recognized that, since with most serum specimens the regression does not go through the zero intercept, per cent digestion in five minutes is not strictly proportional to enzyme concentration. No more precise expression of enzyme concentration, however, could be determined.

Units of amylase:—These are defined as equal to the per cent substrate hydrolyzed in five minutes under the specified conditions of the method.

Lipase time studies:—Hydrolysis of the fat substrate by serum lipase proceeded according to zero order kinetics for 30 to 40 minutes corresponding to 15 to 30 per cent substrate hydrolysis. Results of a typical time study experiment are presented in Figure 3 in which per cent substrate remaining is plotted against time.

Lipase concentration studies:—Hydrolysis of the substrate as a function of lipase concentration was determined for various volumes of serum. An illustrative experiment is presented in Figure 4. A linear regression of per cent substrate hydrolysis on volume of serum was found up to 11.7 per cent substrate hydrolysis, with, in this instance, the regression line passing through the zero intercept. With other serum specimens, however, while the regression was linear, it did not always pass through the zero intercept. Lipase units as calculated from the equation determined in a series of experiments with pancreatic secretion[4] did not offer a better estimate of enzyme concentration.

Units of lipase:—These are defined as equal to the per cent substrate hydrolyzed in 15 minutes under the specified conditions of the method.

Esterase time studies:—Zero order and first order reaction plots of an illustrative time study are presented in Figure 5. Three different components of the

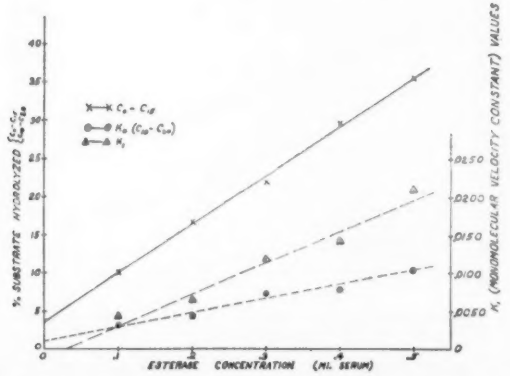

Fig. 6—Hydrolysis of tributyrin substrate as a function of enzyme concentration. Comparison of methods of estimating serum esterase concentration.

zero order curve are discernible, an initial period of rapid hydrolysis during the first three minutes, a period of slightly less active hydrolysis for the next 18 minutes during which there is a rectilinear relationship between degree of hydrolysis and time of incubation, and finally a period of still slower hydrolysis. The monomolecular plot resulted in a curve of similar configuration except that there was only a very slight change in rate of hydrolysis between the second and third periods. This latter finding did not occur in all time studies, in some instances the monomolecular plot being very similar in configuration to the zero order plot. The reaction is a complex one and no single concept of enzyme kinetics explains the over all course of the reaction.

Esterase concentration studies:—Hydrolysis of the substrate as a function of esterase concentration was determined for various volumes of serum. An

illustrative experiment is presented in Figure 6. Inasmuch as the time studies indicated close agreement with both zero and first order kinetics for the period from three to 21 minutes of incubation, the zero (K_o) and first order reaction constants (K_1) calculated from the 10 and 20 minute concentration determinations are presented as well as per cent digestion in 15 minutes ($C_o - C_{15}$). A rectilinear regression on enzyme concentration (volume of serum) is noted with all three concepts of enzyme concentration. None of the three regression lines pass through the zero intercept. Although the zero order and monomolecular regressions approach the zero intercept in this study, in other experiments they failed to do so. Inasmuch as deviations from linearity were least with the per cent digestion in 15 minutes regression, this estimate was adopted as the measure of esterase activity.

Units of esterase:—These are defined as equal to the per cent substrate hydrolyzed in 15 minutes under the specified conditions of the method.

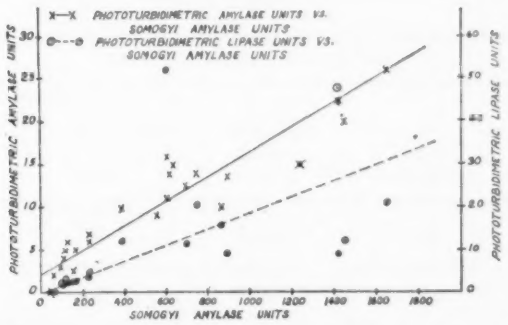

Fig. 7—Correlation between serum amylase concentration estimated by the Somogyi saccharogenic method and serum amylase and lipase concentrations estimated by the phototurbidimetric technics.

Temperature of incubation:—Experiments in which the rate of hydrolysis by the serum enzymes were studied at 25° C., 32° C., and 37° C., revealed that with all three enzymes, the rate of substrate digestion increased with increasing temperature of incubation. Therefore, in order to obtain optimum sensitivity, 37° C. was chosen as the temperature of incubation for each of the methods.

Enzyme stability:—Enzyme determinations performed between one and four hours after drawing the serum, the serum being left at room temperature during this interval, revealed no significant change in amylase, lipase or esterase activity. Storage of serum at —20° C. for 48 hours, however, resulted in a loss of amylase, lipase and esterase activity of 15 to 50 per cent, 50 to 80 per cent, and 10 to 15 per cent respectively. Storage at —5° C. resulted in even greater loss of activity. It is therefore necessary to perform these enzyme determinations on the same day the serum specimen is obtained.

Substrate stability:—Although the substrates remained stable for at least four hours after preparation, storage of all three substrates at —20° C. for 48 hours resulted in significant alteration in their sensitivity to enzymatic hydrolysis. Fresh substrate must be prepared for each day's enzyme determinations.

Duplicate error:—In order to obtain further information concerning the precision of the methods, the magnitude of the duplicate error was determined in studies with different serum specimens. The results are presented in Table I. The magnitude of the error was homogeneously distributed and did not vary with enzyme activity.

Clinical Results

To determine their clinical value, phototurbidimetric amylase, lipase and esterase determinations were performed on sera of normal subjects and of

TABLE I

Duplicate Error of Phototurbidimetric Serum Amylase, Lipase, and Esterase Determinations

Enzyme	No. of specimens	Range of enzyme values (units)	Duplicate error	
			Mean	Standard deviation
Amylase	23	2-22.5	0.5	0.18
Lipase	27	0-12.5	1.0	0.34
Esterase	23	5-62	0.7	0.25

patients with various diseases. The results of these studies are presented in Table II. Group 1, consisting of healthy adults, and group 2, consisting of patients free of disease involving the pancreas, hepatobiliary tract, or salivary glands, form a "combined control group". Disease states in the latter group include cerebrovascular, cardiovascular and respiratory disorders, peptic ulcer, and functional disturbances.

Significantly elevated serum amylase concentrations, ranging from 9 to 26 units, were found only in cases of acute pancreatitis and acute epidemic parotitis. The lowest amylase values in these groups, 9 units, exceeded the highest in the "combined control group". In one patient with Laennec's cirrhosis and in one with infectious hepatitis, an amylase value of 9 was found. In neither of these patients was the serum lipase correspondingly elevated, and the reason for the elevated serum amylase could not be ascertained. Repeat studies revealed amylase values within the normal range in both patients.

TABLE II

PHOTOTURBIDIMETRIC SERUM AMYLASE, LIPASE, AND ESTERASE VALUES IN NORMAL SUBJECTS AND IN PATIENTS WITH VARIOUS DISEASES

Diagnosis	Amylase units				Lipase units				Esterase units			
	No. spec.	No. pts.	Mean	Range	No. spec.	No. pts.	Mean	Range	No. spec.	No. pts.	Mean	Range
1. Healthy adults	10	10	3.8	2-5.5	10	10	1.6	0-2.5	10	10	22.7	19-25.5
2. Controls*	24	23	3.9	0-8.0	47	43	1.8	0-5.5	36	34	13.2	5-22
3. Acute pancreatitis	16	9	15.4	9-26	12	8	22.7	9-52.5	12	8	18.1	7-34
4. Chronic pancreatitis	5	2	2.4	0-4.3	5	2	1.1	0-2.5	5	2	21.7	10.5-38.5
5. Acute epidemic parotitis	2	1	14	10.5-17.5	2	1	2.8	2.5-3	2	1	18.8	18.5-19
6. Laennec's cirrhosis a) with jaundice	6	5	4.6	1-9	12	9	2.7	0.9-5	9	8	8.0	3.3-16
b) without jaundice	8	6	3.5	0-6.5	11	9	2.8	0-6.5	8	6	9.8	7-14
7. Viral hepatitis	5	4	5.6	1-9	5	4	2.7	0.4-5	5	4	15.5	2.5-25
8. Acute cholecystitis	7	4	3.1	1.5-5	7	5	2.3	0.4-6	6	4	15.4	10.5-22
9. Chronic cholecystitis with choledocholithiasis	7	5	3.1	1-6	9	6	1.3	0-2.8	8	6	16.7	11-29
10. Carcinoma a) Pancreas	5	3	3.1	2.5-4	11	6	2.3	0.5-7	8	4	17.3	10.4-22
b) Biliary tract	2	2	1.5	0-3	5	4	1	0-2	4	3	14.3	10.6-17.2
c) Other than a) or b) 1. + liver metastases	2	2	3.4	2.2-4.6	8	8	1.8	0-2.9	7	7	13.4	8.2-16.8
2. No " "	9	7	3.6	1-7	15	14	1.7	0.5-4.5	15	14	12.4	6.2-20.9

*The "control" group consisted of patients free of disease involving the pancreas, hepatobiliary tract, or salivary glands.

Elevated lipase concentrations, ranging from 9 to 52.5 units, were noted only in patients with acute pancreatitis. Neither in the healthy adults nor in any of the other conditions studied was a serum lipase value as high as 9 units obtained.

The serum esterase concentrations were higher in healthy adults than in any of the disease states studied. Other investigators[6] have reported depressed serum esterase activity in chronic debilitating diseases and in acute infectious diseases. Outstandingly low serum esterase concentrations were found in Laennec's cirrhosis, whether or not jaundice was present. These were the only groups in which average values of less than 10 units were found. In one of four patients with viral hepatitis a serum esterase value of 2.5 was obtained. In this patient, who had infectious hepatitis, the serum was obtained at the height of the disease, one day after admission to the hospital. In the other three patients, two with serum hepatitis and one with infectious hepatitis, the serum was obtained during the recovery phase: two during the second to fourth weeks after admission revealed esterase levels of 14 to 18.5 units, and the third during the fourth week after admission revealed an esterase level of 25 units.

None of the three serum enzyme determinations proved to be of diagnostic value in patients with carcinoma. Slightly depressed serum amylase and lipase concentrations were noted in patients with carcinoma arising in the extrahepatic biliary tree. The number of patients studied, however, was too small to allow for any generalizations. Similar enzyme concentration alterations were not noted in carcinoma of the pancreas, in which condition such changes might be expected.

Slightly depressed serum amylase and lipase levels were also noted in patients with chronic pancreatitis. Again, however, the small number of patients studied, and overlapping in range of values with those noted in the "combined control group", prevent any generalizations. No significant alterations in these serum enzyme levels were noted in patients with acute cholecystitis or chronic cholecystitis with choledocholithiasis.

The phototurbidimetric serum amylase and lipase determinations appeared to be of diagnostic value in acute pancreatitis, while the phototurbidimetric serum esterase determination appeared to be of value in the differential diagnosis of jaundice. These two categories were analyzed in greater detail.

Acute pancreatitis:—Nine patients with acute pancreatitis were studied during the period when their serum amylase and/or lipase concentrations determined by standard laboratory procedures, the Somogyi[7] and Cherry and Crandall[8] methods respectively, were significantly elevated. Upper limits of normal in the hospital laboratory for serum Somogyi, and Cherry and Crandall determinations are 180 and 1.5 units respectively. Because of technical factors, there frequently was a delay of several days between the drawing of

the serum specimen and the performance of the phototurbidimetric enzyme technics, the serum being stored at —20° C. during this interval. The standard Somogyi, and Cherry and Crandall procedures were performed by the hospital laboratory on the day the serum was drawn. The results of these studies are

TABLE III

SERUM ENZYME VALUES IN PATIENTS WITH ACUTE PANCREATITIS

Case No.	Somogyi amylase units	Cherry & Crandall lipase units	Phototurbidimetric Determinations			
			No. days delay*	Amylase units	Lipase units	Esterase units
1.	640		1	15		
	620		1	14		
	560		0	9		
2.	602		3	16	52.5	24.5
3.		6.8	0	16	30.5	34
4.	1424	11.2	1	22.5	48	22
	898	4.2	0	13.5	9	18
5.	1430		3	22.5	9	15.5
6.	1250		3	15	30	15
	602		6	11		
7.	866		7	10	16	7
	750		6	14	20.5	9
	388		4	10	12	7
8.	1460		2	20	12	14
9.	1658		2	26	21	25.5
	700		0	12.5	11.5	26

*The number of days elapsing between the drawing of the serum specimen and the performance of the phototurbidimetric enzyme technics is presented in this column (see text for further explanation).

presented in Table III. Because the serum enzyme stability studies failed to reveal a consistent per cent enzyme activity loss for each enzyme, it was not feasible to attempt to correct for loss of activity due to storage. The period of delay in performing the phototurbidimetric tests must be noted in interpreting

the results presented. In spite of this delay, in no instance were either the serum amylase or lipase levels below 9 units.

The same data, plus ten randomly selected studies from the "control" group, are presented graphically in Figure 7. A high degree of correlation (correlation coefficient = 0.944) between the phototurbidimetric and the Somogyi amylase values obtained, specimens having high activities by the standard method also having significantly increased values by the phototurbidimetric method. The correlation between the phototurbidimetric lipase and the Somogyi amylase values was not as good (correlation coefficient = 0.586), there being greater

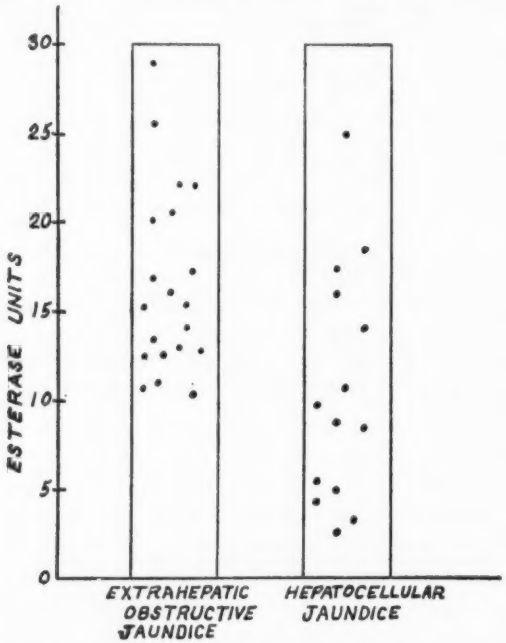

Fig. 8—Comparison of phototurbidimetric serum esterase levels in patients with extrahepatic obstructive jaundice and hepatocellular jaundice.

scattering of the points. There are several possible explanations for this increased scattering including naturally occurring variations in serum amylase and lipase levels, loss of lipolytic activity due to storage of serum, exceeding the upper limits of the turbidimetric method, inherent errors of both methods, *etc.*, and it is not possible to state which are the major factors.

As can be seen in Table III, the serum esterase concentrations fell within the "control" range in nearly all patients, and did not reflect the course of the disease.

Jaundice:—Serum esterase determinations were performed on 24 jaundiced patients, 12 (14 determinations) with hepatocellular jaundice (Laennec's cirrhosis, infectious hepatitis, and serum hepatitis) and 13 (20 determinations) with extrahepatic obstructive jaundice (choledocholithiasis, carcinoma of the head of the pancreas, and carcinoma of the extrahepatic biliary tree). The results are presented in Figure 8. There was considerable overlap between the two groups. In none of the cases of obstructive jaundice, however, was the serum esterase level below ten units, while in eight of the cases of hepatocellular jaundice, the serum esterase level fell below ten units, and in five patients was less than six units. Four of the six serum esterase determinations above ten units in patients with hepatocellular jaundice occurred in the three patients with viral hepatitis previously discussed who were studied during the recovery phase of their disease.

Comment

The validity of the Somogyi method for the determination of serum amylase is well established. The primary advantage of the phototurbidimetric technic herein described is the rapidity with which it can be performed. The substrate is simple to prepare and only a five-minute incubation period is required as compared with a 30-minute incubation period plus time for glucose determinations with the Somogyi method. The finding of significantly elevated serum amylase levels with the phototurbidimetric technic in every instance in which a significant rise was detected with the Somogyi procedure is indicative of the reliability of the method. Only two "apparent false elevations" occurred in over 100 determinations.

The phototurbidimetric amylase technic herein described is very similar to the method of Peralta and Reinhold[9]. Both technics are based on the method originally developed by Waldron[10]. The major difference in these methods is in the interpretation and application of enzyme kinetics. Both Waldron and Peralta used the monomolecular constant as a measure of enzyme concentration. In the present investigation preliminary enzyme kinetic studies revealed that the course of the reaction between ½ and 9 minutes could be as well explained by zero order kinetics as by first order kinetics. In addition, per cent digestion in five minutes proved to be as good a measure of enzyme concentration as the zero or first order reaction constants based on the ½- and 5-minute readings. Therefore, this simpler measurement was chosen as the expression of enzyme concentration.

The most widely used technic for the determination of serum lipase is the method of Cherry and Crandall[8]. The chief disadvantage of this method is the 24-hour incubation period required to complete the determination. The phototurbidimetric technic herein described requires only a 15-minute incubation period. No "false lipase elevations" occurred in over 100 determinations. In every case of acute pancreatitis in which either the Somogyi amylase or the

Cherry and Crandall lipase levels were elevated, a significant rise in serum lipase was detected with the phototurbidimetric technic. It has been reported that in acute pancreatitis serum lipase concentrations may remain elevated after the serum amylase has returned to normal[11]. This was not found to be the case in the present study, since the course of the serum lipase concentration closely paralleled that of the serum amylase concentration, and both serum enzymes returned to normal levels in one to four days.

Esterases are defined as enzymes which split organic esters of low molecular weight, and lipases as enzymes which split glycerol esters of fatty acids of high molecular weights, *i.e.*, fats. This division is only relative. Esterases have generally been regarded as originating mainly in the liver, while lipases come primarily from the pancreas[12]. The results of the present study indicate a high degree of specificity of the lipase and esterase substrates. In acute pancreatitis with elevated serum lipase levels, as determined by standard procedures, there was increased hydrolysis of the fat (lipase) substrate but not of the tributyrin (esterase) substrate. In severe hepatocellular disease in which one might anticipate reduced serum esterase levels[6], there was decreased hydrolysis of the tributyrin substrate, but hydrolysis of the fat substrate remained unchanged. Thus there appears to be a distinct separation of serum lipase and esterase by the substrates used in this study.

The phototurbidimetric serum esterase procedure proved to be of value in the differential diagnosis of extrahepatic obstructive jaundice and hepatocellular jaundice. Vorhaus and Kark[6] have also reported depressed serum esterase (cholinesterase) levels in hepatocellular disease, and normal levels in patients with obstructive jaundice. Early in acute hepatitis, they found low serum cholinesterase levels, and as the patient improved, the serum cholinesterase rose to normal levels. In the present study a low serum esterase value was obtained in only one of four patients with viral hepatitis. This low value was found in the only patient studied early in the course of the disease. Williams et al[13] observed lower serum cholinesterase values in patients with carcinoma with hepatic metastases than in those with nonhepatic metastases. In the present study there was no significant difference in esterase levels between patients with metastatic carcinoma, whether or not hepatic metastases were present, and patients in the "control" group. While pathologic evidence of hepatic metastatic involvement was obtained in every such case, no attempt was made to quantitate the degree of involvement and correlate it with serum esterase levels. This plus the use of a substrate which is not specific for cholinesterase, and hence not as sensitive to alterations in serum cholinesterase levels, might account for the failure of the present study to confirm William's findings. Analysis of the liver function tests in patients with chronic liver disease failed to reveal that any one test correlated more closely with esterase levels than any other. In general, however, as has been noted by others[6], low serum esterase concentrations were usually associated with low serum albumin levels.

Summary

1. Serum amylase, lipase and esterase levels in health and in various disease states were determined by modifications of previously described phototurbidimetric technics. In comparison with standard analytic methods, these procedures had the advantage of simplicity and rapidity while still maintaining a high degree of specificity and accuracy.

2. Preliminary kinetic studies revealed that under the conditions of the procedure with the lipase method the reaction proceeded according to zero order kinetics, but with the amylase and esterase methods no single concept of enzyme kinetics explained the over all course of the reaction. Nevertheless, with all three methods, per cent digestion per unit time afforded an adequate measure of enzyme concentration.

3. Significantly elevated serum amylase levels were found only in acute pancreatitis and acute epidemic parotitis. Only two "apparent false elevations" occurred in over 100 determinations. In every instance in which a significant rise in serum amylase concentration was detected with the Somogyi saccharogenic procedure, significantly elevated levels were obtained with the phototurbidimetric technic.

4. Significantly elevated serum lipase levels were noted only in acute pancreatitis. No "false lipase elevations" occurred, and in every case of acute pancreatitis in which either the Somogyi amylase or the Cherry and Crandall lipase levels were elevated, a significant rise in serum lipase was detected with the phototurbidimetric technic.

5. Serum esterase concentrations were higher in healthy adults than in any of the disease states studied. Significantly depressed esterase levels were obtained in Laennec's cirrhosis, and early in the course of viral hepatitis. This finding was of value in the differentiation of hepatocellular from obstructive jaundice, there being no significant alteration in serum esterase in obstructive jaundice.

Acknowledgment

The author is indebted to Mrs. Elaine Sadler for her invaluable technical assistance.

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SPONTANEOUS PERFORATION OF THE ESOPHAGUS IN HODGKIN'S DISEASE

Report of Three Cases and Literature Review

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Introduction

Intrinsic involvement of the esophagus in patients with Hodgkin's disease is rare[1-5]. In an extensive world literature review in 1957, Delaunoy found only 17 cases[6]. None have been reported since that time. Of this group he cited two cases of spontaneous esophageal perforation, both of which had appeared in the foreign literature[7,8]. The first case of esophageal perforation was described by Pesonem[7] in 1938. This was an autopsy case revealing a tracheoesophageal fistula. Carcinoma was suspected. Histologic sections showed Hodgkin's disease. The second case was reported by Leroux-Robert, et al[8] in 1951. This patient was a 25-year old white female who developed dysphagia. An x-ray examination revealed perforation of the esophagus at the level of D4-D5. Esophagoscopy and biopsy were accomplished. Histologic sections showed Hodgkin's disease. Symptoms disappeared and x-ray examination of the esophagus was negative following local deep x-ray therapy. To our knowledge, spontaneous perforation of the esophagus due to Hodgkin's disease has never been reported in the English literature.

The autopsy files in the Department of Pathology here at the Ohio State University were reviewed covering the years 1937-1959. The diagnosis of Hodgkin's disease was established in 170 patients. As shown in Table I, gastrointestinal involvement occurred in 26 (15.3 per cent). The esophagus was involved 5 times, stomach 10 times, duodenum 3 times, jejunum once, ileum 3 times, "small bowel" 8 times, appendix once, and colon 5 times. Over half of these patients exhibited mucosal ulcerations. Of the 5 patients with esophageal involvement, 1 showed spontaneous perforation, as demonstrated by a bronchoesophageal fistula. This case will be described in detail as one of the case reports. Gross and histological findings in the other 4 patients were submucosal infiltration in 2, nodular infiltration (tumor) in the muscularis and adventitia in 1, and periesophageal infiltration in 1.

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The purpose of this paper is to present 3 patients with established generalized Hodgkin's disease who developed spontaneous esophageal perforation. Pathogenesis, diagnosis, and treatment will be discussed.

Case Reports

Case 1:—C.E. (OSUH #473932), a 35-year old white female, was first admitted to University Hospital in June, 1942. The diagnosis of Hodgkin's disease was made by cervical lymph node biopsy. Deep x-ray therapy was given to the cervical and mediastinal lymph nodes. She was asymptomatic until January, 1947, when *dysphagia* developed and persisted. In March, 1947, a course

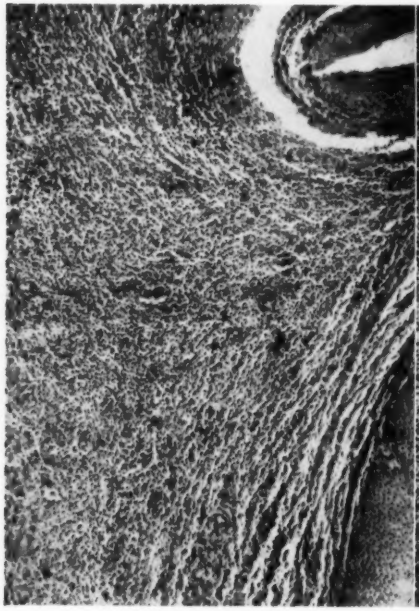

Fig. 1

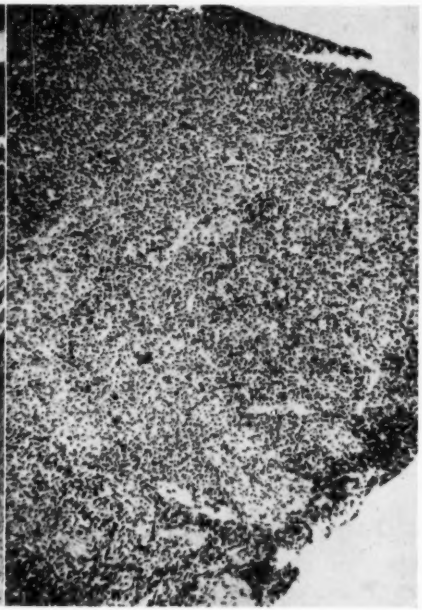

Fig. 2

of nitrogen mustard was given with abatement of dysphagia. One month later dysphagia recurred together with anterior chest pain, chills and fever, and a cough productive of purulent sputum. Another course of nitrogen mustard was given. Symptoms persisted. Therefore she was admitted for the fourth time May, 1947, at which time x-ray examination of the esophagus revealed a fistula from the esophagus to the left main stem bronchus. In spite of active therapy, death occurred one week later.

Postmortem examination revealed generalized Hodgkin's disease. There was a large necrotic ulcer on the anterior esophageal wall just distal to the carina

with a 1 cm. diameter fistula communicating with the left main stem bronchus. There were no enlarged lymph nodes in the immediate vicinity. Histologic sections revealed Hodgkin's disease of the esophagus (Fig. 1) and bronchus.

Case 2:—L.B. (OSUH #490780A), a 45-year old colored female, was first admitted to University Hospital in February, 1949. The diagnosis of Hodgkin's disease was made by mediastinal lymph node biopsy. Deep x-ray therapy was given to the mediastinum. She became asymptomatic and did well until April, 1956, at which time she received x-ray therapy to enlarged cervical lymph nodes with good results. Sore throat and *dysphagia* developed in January, 1958. Symp-

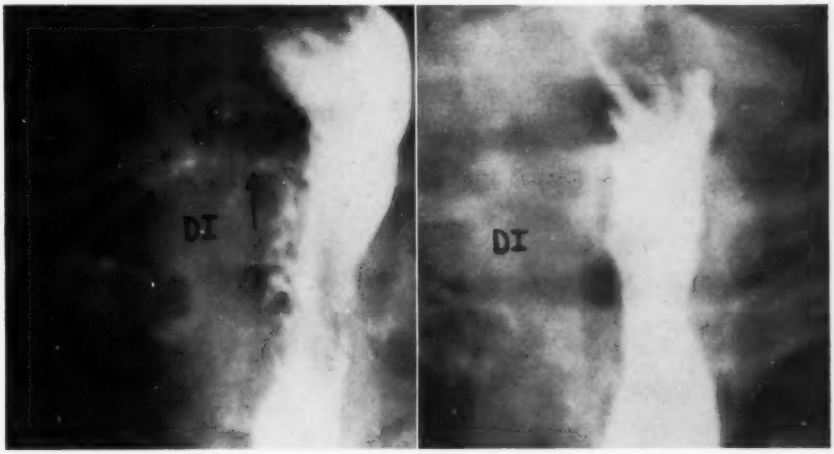

Fig. 3a Fig. 3b

toms persisted in spite of symptomatic measures. An x-ray examination was performed in April, 1958 and revealed perforation of the esophagus at the level of D1-D2. Esophagoscopy was performed and revealed narrowing of the esophagus just distal to the cricoid. The mucosa was reddened and polypoid granulomatous tissue appeared to project into the lumen. Biopsy was accomplished. Histologic sections showed Hodgkin's disease (Fig. 2). Local deep x-ray therapy was given. Dysphagia disappeared. An x-ray examination of the esophagus was normal 2 weeks later. Figure 3 compares x-rays of the esophagus before and after x-ray therapy.

This patient was asymptomatic until 20 August 1959, at which time dysphagia recurred. An x-ray examination of the esophagus was performed and revealed infiltration and perforation of the esophagus at the level of C7-D1. She was admitted to the hospital on 4 September 1959, at which time esophagoscopy was performed and revealed narrowing of the cervical esophagus and some

localized ulceration. A biopsy was accomplished and exhibited characteristics of Hodgkin's disease. Local deep x-ray therapy was given. She was discharged 19 September 1959, relatively asymptomatic. A repeat x-ray of the esophagus was performed one month later and reported as normal. Dysphagia had disappeared.

Figure 4 compares x-rays before and after x-ray therapy.

Case 3:—E.R. (OSUH #572178), a 65-year old white male veterinarian, was first admitted to University Hospital in October, 1955. The diagnosis of Hodgkin's disease was made by supraclavicular lymph node biopsy. Deep x-ray therapy was given to the supraclavicular and mediastinal lymph nodes. An

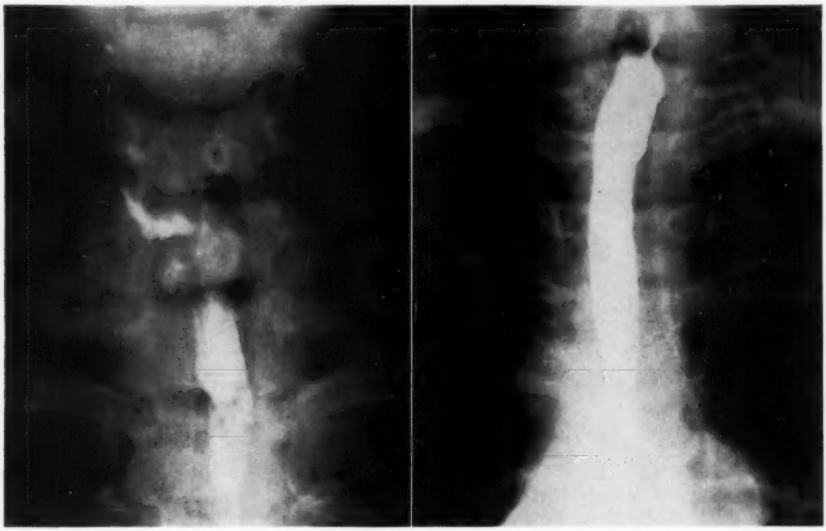

Fig. 4a Fig. 4b

upper gastrointestinal series was normal at that time. In August, 1956, x-ray therapy was given to a tumor mass occupying the middle lobe of the right lung. *Dysphagia* developed in January, 1957. This persisted for 8 months in spite of symptomatic therapy. An x-ray examination of the esophagus was normal at that time. In May, 1958, x-ray therapy was given to the deep iliac lymph nodes in an effort to relieve massive edema of the lower extremities. This persisted. Therefore he was hospitalized in June, 1958, and given a course of nitrogen mustard.

In September, 1958, anorexia and epigastric pain developed. These persisted and in November, 1958, he experienced a rather severe bout of epigastric pain

lasting several hours. Four days later an outpatient upper gastrointestinal series was performed and revealed a perforation of the lower esophagus with a fistulous tract leading through the diaphragm to a subdiaphragmatic abscess (Fig. 5). There was no evidence of mediastinitis. He was hospitalized immediately and a course of deep x-ray therapy was given to the lower esophagus. Esophagoscopy and biopsy were not accomplished because he was too ill. Antibiotics and blood transfusions were given as supportive measures. Incision and drainage of the abscess was performed.

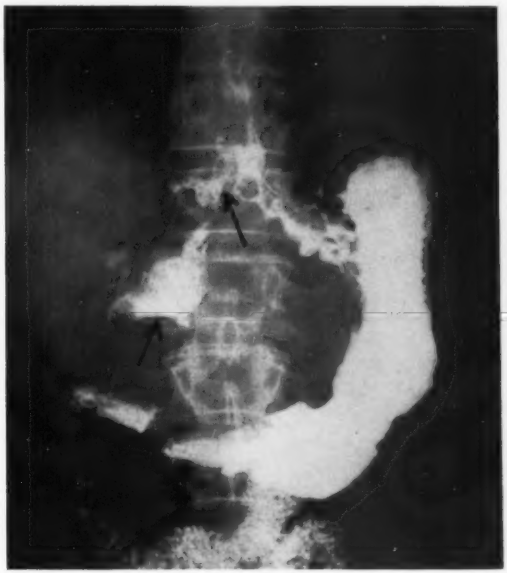

Fig. 5

His hospital course was characterized by complications: right lower lobar pneumonia while on 3 gm. of chloromycetin daily, esophagocutaneous fistula, right empyema requiring medical and surgical drainage on two occasions, pleurocutaneous fistula, and hepatic abscess with a cutaneo-hepatic-biliary fistula. Cultures from these various areas revealed coagulase positive *Staphylococcus aureus*. All of these complications were overcome and his Hodgkin's disease apparently became quiescent. All fistulas closed. He was discharged ambulatory 23 January 1959, relatively asymptomatic.

A later communication from his family doctor revealed that he had died 13 April 1959, from what appeared to be a resurgence of his basic disease. An autopsy was not performed.

Comment

The three cases presented herein represent an extremely rare complication of Hodgkin's disease. All three patients had a history of established generalized disease. The esophagus was the only part of the gastrointestinal tract that was involved. Dysphagia was the common symptom. This developed 4, 5, and 23 months before the diagnoses of perforation were made. An x-ray examination of the esophagus was performed in only 1 patient prior to perforation (Case 3). Two patients (Cases 1 and 3) had received nitrogen mustard 1 and 5 months before perforation occurred. None of these patients were subjected to esophagoscopy prior to perforation. Two patients (Cases 2 and 3) responded well to local deep x-ray therapy with subsequent closure of the perforations. Figure 3 exhibits this nicely.

TABLE I

Autopsy Series

170 Patients with Hodgkin's Disease, Ohio State University, 1937-1959

Gastrointestinal Involvement	26 (15.3%)		
Esophagus	5	Infiltration	4
		Perforation	1
Stomach	10	Infiltration	9
		Ulcer	1
Duodenum	3	Infiltration	1
		Ulcer	2
Jejunum	1	Infiltration	1
Ileum	3	Infiltration	1
		Perforation	2
"Small Bowel"	8	Infiltration	8
Appendix	1	Infiltration	1
Colon	5	Infiltration	5

Hodgkin's disease of the gastrointestinal tract usually begins as a nodular infiltration in the submucosa. This infiltration may extend to the lumen or it may extend to involve the adventitia and serosa. Some narrowing of the lumen generally occurs. Mucosal ulcerations are frequent. The regional lymph nodes are almost always involved. Any site in the gastrointestinal tract may become involved in this manner[1]. This infiltration would of necessity cause weakness of the gastrointestinal wall and subsequent tissue hypoxia. Patients with Hodgkin's disease are often toxic and in negative nutritional balance. Leukopenia, anemia, and thrombocytopenia occur not infrequently because of the basic disease and/or therapy. Superimposed infections are not uncommon. These are but some of the factors contributing to decreased tissue resistance. Therefore the

possibility of perforation would be greater than in the normal individual under a wide variety of circumstances: mechanical effects of peristalsis, endoscopy, and ingested material; corticosteroid therapy; peptic ulceration from aberrant gastric tissue; other local gastrointestinal lesions; traction, pressure, or infiltration from regional lymph nodes; and possibly nitrogen mustard therapy. Concerning the latter, we have observed 2 patients who developed perforation of the cecum within 3 days after receiving a course of nitrogen mustard. Surgical closure was accomplished in both patients with good results. Biopsies were taken at the sites of perforation and histologic sections revealed Hodgkin's disease. The cause of the perforations was thought to be the rapid breakdown of infiltrative cells following nitrogen mustard.

From this experience we may learn that the development of dysphagia in any patient with Hodgkin's disease warrants immediate, thorough, and frequent investigation. Serial x-ray examinations of the esophagus are indicated. If a lesion is demonstrated, esophagoscopy and biopsy should be accomplished if possible and histologic study performed. The treatment of choice seems to be local deep x-ray therapy.

Summary and Conclusions

Three cases of spontaneous perforation of the esophagus due to Hodgkin's disease are presented. These represent the only reported cases in the English literature. In an extensive literature review, only 2 such cases have been reported, both of which were in the foreign literature.

The common symptom of esophageal involvement was dysphagia. This requires prompt investigation utilizing x-ray examination, esophagoscopy, and biopsy.

The treatment of choice seems to be local deep x-ray therapy.

In our autopsy series of 170 patients with Hodgkin's disease, gastrointestinal involvement occurred in 26 (15.3 per cent). The esophagus was involved in 5 (2.9 per cent) of these patients.

Only 17 cases of esophageal involvement due to Hodgkin's disease have been reported in the literature. This report brings the total to 24, five of which exhibited spontaneous perforation.

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SOME RECENT STUDIES IN THE IMMUNOLOGY OF HEPATITIS

I. Detection of Soluble Antigens in Sera of Hepatitis Patients by Use of the Schultz-Dale Reaction

JACK G. MAKARI, M.D., D.T.M.&H., Sc.M.*

Plainfield, N. J.

The problem of early detection of antigen in viral and rickettsial diseases is of great academic and clinical interest. Immunologic methods aimed at the detection of viral and rickettsial antibodies have been only partially successful. These detect bivalent but not univalent antibodies. Moreover, since antibodies appear late in the disease, their use as a diagnostic tool in these acute diseases has serious limitations. In such diseases, however, the search for antigens, instead of antibodies, assumes a much greater significance, and if successful, it could point to the nature of the disease process in its early phase and consequently to the proper method of treatment of such a disease. Earlier attempts to devise a specific serologic test in patients with viral hepatitis by using precipitation and complement fixation methods have been reviewed by Havens et al[1] and Havens and Eichman[2]. According to these authors, certain workers have failed to substantiate the positive results of others and most of these reactions were thought to be "nonspecific and of no practical value".

In some previous unpublished experiments done in 1951, referred to by Snyder[3], we found that guinea pigs could be sensitized to rickettsial antigens by the help of Freund's adjuvants, so that their excised uterine horns would contract specifically in the presence of rickettsial antigen in a Schultz-Dale bath. Although the sensitivity of this method was not superior to a modified complement fixation method studied at Dr. Snyder's laboratory, it soon became evident that with the modified Schultz-Dale method, a mixed antigen could easily be separated into its antigenic components (by desensitization procedures). Rickettsial and egg yolk antigens, for example, could easily be distinguished by this technic.

It was thought desirable to use the same approach for the detection of a possible antigen from the sera of patients with hepatitis. At the same time an attempt was made to increase the sensitivity of this method by the use of a smaller Schultz-Dale bath, i.e. 10 ml. instead of 40 ml.

The finding of the ascitis-hepatitis-agent of mice (AHA) by Jordan and Mirick[4] afforded an opportunity for the study of possible common antigenic relationships between AHA in mice, and infective hepatitis (IH) and serum hepatitis (SH) in man. Should such relationships be established, this phenomenon might well serve as a basis for a diagnostic test in man.

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This work was done during 1952 and 1953 at the Biological Division of the Department of Medicine of the Johns Hopkins Hospital. The same method was later successfully utilized by us[5,6,7] for the detection of carcinoma antigens in the sera of patients with carcinoma. In this latter case, the test was positive in 96.8 per cent of proved carcinoma cases and in only 4 to 5 per cent of patients with other diseases. Burrows[8] has recently confirmed these findings. He obtained 96.7 per cent positive tests in proved carcinoma cases and only 3.3 per cent positive tests in patients with other diseases and other tumors.

This study reports the use of the Schultz-Dale reaction for the detection in the sera of human hepatitis cases of antigens in common with the ascitis-hepatitis-agent (AHA) of mice.

Materials and Methods

Pooled 10 per cent liver-spleen-kidney (LSK) homogenates and later 50 per cent ascitic fluid from mice infected with AHA of mice were used for immunization of guinea pigs. These antigens were extracted with ether over night at 5° C. The material in suspension was then removed and the remaining solution de-etherized. It was then injected with Freund's adjuvants subcutaneously into virgin female guinea pigs, weighing between 300 to 400 gm. in the following proportions:

AHA	.4 ml.
Mineral oil	.4 ml.
Falba	.2 ml.
Mycobacterium butyricum	.14 mg.

In 4 to 6 weeks, the guinea pigs were sacrificed for testing. In some cases a repeat dose of antigen with adjuvants was given and two weeks later, the pigs were killed and the uterine horns excised and used in a Schultz-Dale apparatus. The Schultz-Dale apparatus and the method of testing has been described in detail elsewhere[5].

Reactions of the sensitized uterine muscle were then released by the addition of normal LSK antigen (prepared from healthy mice homogenates in the same way as the AHA antigen). This was repeatedly added to the bath in .1 ml. amounts, until the horn became desensitized to it. Following this procedure desensitization to human serum was done by adding it to the Schultz-Dale bath in .5 ml. amounts. A properly sensitized uterine horn should not contract when normal Group "O" serum is added to the bath (negative serum control). It should specifically contract, however, when a known hepatitis serum or when AHA antigen is added (positive serum control). Horns not properly sensitized were discarded.

For a serum to be a true positive, it should be possible by repeated additions, to desensitize the horn to it (due to the neutralization of the antibodies

coating the uterine muscle by specific antigens in the serum added). Inability to desensitize completely or in part the horn to the serum in question, indicates the presence of a pressor substance in the serum which is affecting the horn in a nonspecific fashion. This latter is considered a false positive reaction.

Passive sensitization was done by immersing normal unsensitized guinea pig uterine horns in a serum-tyrode mixture from a guinea pig or a rabbit actively immunized with AHA. Contact was allowed for 30 minutes at 0°C.

The results of the test were recorded in terms of contraction index (CI). This was obtained by dividing the specific contraction of the horn in mm. (produced in response to the addition of the serum in question) by the amount of contraction of the same uterine horn produced by 10r of histamine base. Scoring was done as follows:

	Reaction time	
Contraction index	*1st 2½ min.*	*2nd 2½ min.*
.5 - 1	++++	+++
.2 - .49	+++	++
.1 - .19	+	0
0 - .09	0	0

The cases studied comprised the following groups:

I. Patients hospitalized at the Johns Hopkins Hospital. Their sera were examined either fresh or after it had been kept frozen in a CO_2 ice chest (at —40° C). These included not only cases of IH and SH, but also liver cirrhosis, other diseases, pneumonia, etc.

II. Twenty volunteers at the Maryland State Reformatory for Males, being studied by Leftwitch, Mirick, and Henle[9]. These will be reported on in detail in another paper. In this study only their preinoculation sera will be referred to.

III. Cases from the Cancer Detection Clinic at the Johns Hopkins Hospital exhibiting no apparent signs of jaundice.

Results

Common antigenicity between AHA of mice and hepatitis in man:—Antigens prepared from mice infected with the ascitis-hepatitis-agent (AHA) exhibit a wide antigenic spectrum with components in common with the sera from patients with infective hepatitis (IH) and serum hepatitis (SH) of man, and with an antigen prepared from a mouse with spontaneous jaundice.

Results of desensitization studies reported in Table I show that IH and SH antigens are distinct and separate antigenically from each other and from the LSK antigens found in control healthy mice. A third distinct antigen was found

TABLE I

DESENSITIZATION STUDIES USING THE SCHULTZ-DALE METHOD. GUINEA PIGS IMMUNIZED WITH ANTIGENS PREPARED FROM EITHER LIVER-SPLEEN KIDNEY HOMOGENATES OR FROM ASCITIC FLUID CONTAINING ASCITIS-HEPATITIS-AGENT (AHA) OF MICE

Case No.	Releasing antigen (added to bath)	Schultz-Dale reaction	Antigen postulated	Interpretation of result
Case 1	LSK–Normal	–		Common antigens exist between AHA of mice and those in the sera from C.B., IH and SH of man. Desensitization was not done in this case.
	C.B.–Serum	++++	I	
	LSK–Normal	–		
	SH–Serum	++++	II	
	LSK–Normal	–		
	IH–Serum	++++	I	
Case 2	LSK–Normal	–		IH and SH sera have separate antigens.
	Gr. O–Serum	–		
	Klugermann–IH Serum	++++	I	
	Klugermann–IH Serum	–		
	Schleigh–SH Serum	++++	II	
Case 3	LSK–Normal	–		IH and SH sera have different antigens.
	Gr. O–Serum	–		
	Hall–IH Serum	++++	I	
	Hall–IH Serum	–		
	Sterling–SH Serum	++++	II	
Case 4	Gr. O–Serum	–		1. C.B. and IH are alike but distinct from SH,LSK and spontaneous jaundice of mice.
	C.B.–Serum	++++	I	
	C.B.–Serum	++++		
	C.B.–Serum	+		
	C.B.–Serum	–		
	Klugermann–IH	+	I	2. Spontaneous jaundice (mice) has a component in addition to IH and SH (i.e. component III).
	Schleigh–SH	++++	II	
	Schleigh–SH	–		
	LSK–Normal	++++		
	LSK–Normal	+		
	LSK–Normal	–		3. AHA has no additional components to I, II, III, & IV.
	Spont. Jaundice–Mice	++	I & III	
	Spont. Jaundice–Mice	–		
	AHA antigen	–	I, II, III	
Case 5	LSK–Normal	–		1. All three IH cases have one antigen in common which is distinct from Hodgkin's case or SH.
	Gr. O–Serum	–		
	Strong–IH Serum	++++	I	
	Stokes–IH Serum	+++		
	McDaniel–IH	–	I	
	Hubbard–Hodgkin's	++++	III	2. Hubbard–Hodgkin's with jaundice has another antigen distinct from both IH and SH.
	Hubbard–Hodgkin's with jaundice	–		
	Schleigh–SH	++++	II	

TABLE I *(Continued)*

DESENSITIZATION STUDIES USING THE SCHULTZ-DALE METHOD. GUINEA PIGS IMMUNIZED WITH ANTIGENS PREPARED FROM EITHER LIVER-SPLEEN KIDNEY HOMOGENATES OR FROM ASCITIC FLUID CONTAINING ASCITIS-HEPATITIS-AGENT (AHA) OF MICE

Case No.	Releasing antigen (added to bath)	Schultz-Dale reaction	Antigen postulated	Interpretation of result
Case 6	Gr. O—Serum	+++		1. Antigens in Jones (pneumonia) and Sanford (cirrhosis) seem to be similar to IH (Ag I).
	Gr. O—Serum	−		
	Clark—pneumonia	−		
	Sanford—cirrhosis	++++	I	
	Jones—pneumonia	++++	I	
	Lawman—pneumonia	−		2. Sweet, a case of pneumonia with fatty infiltration, has an antigen distinct from IH and SH.
	Segoria—hepatitis	−		
	Boyken—cirrhosis	−		
	Ogelsby—cirrhosis	−		
	Whealer—IH	−		3. Spontaneous jaundice of mice has no antigens besides I, III and LSK.
	Sweet—pneumonia with fatty liver	++++ −	III	
	LSK—Normal			
	Spont. Jaundice—Mice	−	I, III	4. SH has an additional component to I, III, and LSK (i.e. II).
	Klugermann—IH	−	I	
	Schleigh—SH	++++	II	
Case 7	Gr. O—Serum	−		Spontaneous jaundice of mice desensitizes to IH (Ag I) but not to SH (Ag II); SH component is missing in it.
	LSK—Normal	−		
	Spont. Jaundice—Mice	++++	I, III	
	Whealer—IH	−	I	
	Klugermann—IH	−	I	
	Schleigh—SH	++++	II	
Case 8	Gr. O	−		Spontaneous jaundice of mice is not desensitized by IH (Ag I). It should have other antigens besides I and LSK.
	Stokes—IH Serum	++++	I	
	LSK—Normal	−		
	Spont. Jaundice—Mice	++++	I, III	
Case 9	Gr. O	−		1. SH (Ag II) and IH (Ag I) are different.
	Schleigh—SH	+++	II	
	Lawman—pneumonia	−		2. Saunders pneumonia has probably an antigen related to IH (Ag. I).
	Gillette—tuberculosis	−		
	Klugermann—IH	++++	I	
	Saunders—pneumonia	+++	I	
	Saunders—pneumonia	−		3. Spontaneous jaundice of mice has an additional antigen to IH and SH (i.e. Ag. III).
	Klugermann—IH	−	I	
	Schleigh—SH	−	II	
	C.B.—IH	−	I	
	Spont. Jaundice—Mice	+++	I, III	4. AHA has no other antigens besides LSK, II, I, and III.
	Spont. Jaundice—Mice	−		
	AHA	−	I, II, III	

in a case of pneumonia with fatty infiltration of liver (Sweet) and likewise in a case of Hodgkin's disease (Hubbard). These antigens have been designated as antigens I (IH), II (SH), III (Sweet-Hubbard) and LSK. It was not determined whether this Antigen III was the same in both Sweet and Hubbard.

An antigen present in the original serum of C.B. (a pathologist who died at Johns Hopkins Hospital after cutting his finger while autopsying two patients with diffuse liver necrosis and who was found at autopsy to have acute necrosis of liver) proved to be similar to IH (Antigen I). This is of interest because AHA was discovered in mice receiving urethane in their drinking water following the serial intraperitoneal passage of extracts of the liver of this patient[4]. Was this an adapted human virus or was it a dormant agent, activated by this procedure?

Table II shows the distribution of these antigens in the hepatitis of man and mice studied. The three human antigens found had only one component each, besides the normal LSK component. In the spontaneous jaundiced mouse, two components were found (in addition to LSK) while in AHA three components were identified (in addition to LSK). The broader antigenic spectrum of AHA would thus favor its being a mouse disease rather than an adapted human strain. A similar conclusion was reached by Mirick[10]. Hepatitis agents of viral origin have been demonstrated in mice by Gledhill and Andrewes[11] and others. Most workers in this area seem to agree that these are latent mouse viruses and that "the presence of such agents is a likely consequence of the blind passage emergence of a dormant agent[12]". Furthermore, the antigenic similarity of the original C.B. antigen to IH indicates that it is a human type. Of interest was the finding that Antigen III was present in the serum from SH as well as AHA but not from IH, the spontaneous jaundiced mouse, or the pneumonia or Hodgkin's cases studied. This may represent a special adaptation to an abnormal entry where an artificial route (i.e. injection) is necessary for infection.

Presence of antigens in human sera in common with AHA of mice:—The finding of common antigenicity between IH and SH in man and AHA in mice is not surprising. Common antigenicity, for example, between human plasmodia and that of lower animals is well established[13,14,15].

Table III shows the results obtained with the sera of 100 individuals where detection of antigens in common with AHA of mice was done by the Schultz-Dale method. Only the first bleeding from each patient was recorded.

Of 19 cases of infective hepatitis (IH) tested, 18 (i.e. 95 per cent) were positive and so were all of the six hepatitis (SH) cases studied. The one IH serum (out of 19) which gave a negative reaction, was tested only after several days of storage in the ice chest at 5° C. All others were kept frozen at —40° C in carbon dioxide ice. Also another serum from patient (N) which showed a positive reaction when first tested became negative after storage at 5° C for the same period.

In the 17 cases with pneumonia and chronic hepatocellular disease, 50 and 56 per cent respectively gave positive reactions. In the five cases with *lupus*, tuberculosis and obstructive jaundice no positive reactions were observed while only one out of the 20 volunteers tested from the Maryland State Reformatory gave a positive reaction. A year before this volunteer had received an oral inoculation of egg-passage material containing hepatitis virus. Of the 33 cancer detection clinic patients tested, 24 per cent showed positive reactions. The mean percentage for both cancer detection clinic patients and volunteers is 16 per cent.

Comment

In evaluating the usefulness of a test for a specific disease, we have been made to believe that it is even more important to find out the extent of the

TABLE II

Distribution of Antigens in Hepatitis of Man and Mice

Disease	Host	Ag. I	Ag. II	Ag. III	LSK
Infective hepatitis	Man	+	−	−	+
Serum hepatitis	Man	−	+	−	+
Pneumonia with fatty infiltration of liver and Hodgkin's with jaundice	Man	−	−	+	+
Spontaneous jaundice	Mouse	+	−	+	+
Ascitis-hepatitis-agent	Mouse	+	+	+	+

so-called false positivity of such a test, i.e. where the test is positive but the clinical impression does not point to the disease, than its degree of sensitivity in detecting clinically known cases. If the so-called "false positivity" of the test is more than we like to see, we immediately discard the test and label it as nonspecific regardless of how high its sensitivity is.

This is no doubt a biased state of affairs since most diseases behave like an iceberg with the clinically apparent cases representing a much smaller fraction of the total disease than the inapparent ones. We should be prepared, therefore, to encounter many more of these inapparent cases where the individual looks clinically healthy, but in whom the causative agent of disease or its related antigens are present in the blood. It follows, therefore, that it is much more important to emphasize the sensitivity of such tests rather than their "false positivity".

Three of the cases studied emphasize this point. The first is the "healthy" volunteer with the positive test. A year before this volunteer had received an oral inoculation of egg-passage material containing hepatitis virus. As a result of this experimental infection, he had developed hepatitis the year before. Is the positive Schultz-Dale test a year later to be considered a "false positive"? Could it not be that this is a true positive test, an indicator of the presence of a latent virus from the year before?

Of interest is the finding that two out of the eight positive reactors in the Cancer Detection Clinic cases were a husband and his wife. The wife gave no history of hepatitis but when questioned, the husband gave a history of previous hepatitis. He also stated that he had been refused as a blood donor by the Red Cross for that reason. Are we to consider these two cases as "false positives" just because they look healthy? Or are we to think more in terms of subclinical infections and healthy carriers in viral disease? Stokes[16] records four instances in which the wives who were infected appeared to have contracted the disease from their husbands. It may well be that subclinical infections under similar conditions are much more prevalent. Stokes even wondered about the possibility of venereal transmission in hepatitis.

We have been accustomed to think of cause and effect, of virus and disease, and therefore, the existence of a virus without disease has been doubted and its possible wider distribution in man than is apparent through clinical manifestations, has been ignored. Yet we are finding in "healthy" blood donors, more and more carriers of the viral agent of hepatitis capable of infecting other hosts. Stokes[17] states that none of the seven carriers of hepatitis virus which they studied had a history of actual jaundice. He thought there must be many hundreds or even thousands of such carriers. Other workers refer to the significance of the carrier state in other viral diseases. Thus Hammon[18] points to the occurrence of a carrier state in immune individuals in poliomyelitis. Von Magnus[19] goes further to differentiate complete active forms of the influenza virus in which infectivity and antigenicity are retained, and inactive or incomplete forms where infectivity is lost while antigenicity is preserved. It is also well known that subclinical infections do take place. These are thought to be caused by viral strains of low virulence which do not cause clinically apparent disease but which are still good antigens in inducing a state of immunity in the host, and in being detectable by such immunologic procedures as the Schultz-Dale method.

The question arises as to the high incidence of positive reactors in cirrhosis and pneumonia (50 and 56 per cent). Is this to be taken as a loss of specificity of the test or is this a demonstration of the inadequacy of some of our present concepts in regard to hepatitis in particular and to host-viral relationships in general?

If we accept the concept that a hepatitis virus of low virulence is perhaps more widely distributed in populations, and that it is circulating in the blood in an inactive or dormant phase, it is conceivable that such an inactive virus could, under certain conditions, adsorb to certain tissues of the host (such as liver and lung), where the circulating virus comes in immediate contact with endothelial lining. Could it not be also that under certain pathologic conditions with a lowering of resistance (i.e. acute infection of lungs or changes leading to chronic cirrhosis of liver or to Hodgkin's disease), such an adsorbed virus could be released back to general circulation?

Could this not explain the finding of an IH-like antigen (Antigen I) in the serum of 50 to 56 per cent of patients with pneumonia and cirrhosis? Could this

TABLE III

RESULTS OF THE SCHULTZ-DALE REACTION FOR HEPATITIS ANTIGENS IN 100 INDIVIDUALS (FIRST BLEEDING ONLY)

Disease	Total cases	Result of Schultz-Dale	
		Positive reactions	% Positive reactions
Infective hepatitis IH	19	18	95
Serum hepatitis SH	6	6	100
Pneumonia	8	4	50
Cirrhosis	9	5	56
Obstructive jaundice *lupus*, tuberculosis	5	0	0
Cancer detection clinic patients	33	8	24
Volunteers	20	1	5

not explain also the finding of Antigen III in Sweet—a pneumonia case, and Hubbard—a Hodgkin's case?

Furthermore, it is to be stressed that our findings of a high incidence of Schultz-Dale reactors to AHA antigens of mice in pneumonia and chronic liver disease is similar to the finding of antibodies by other workers (see Table IV).

Havens and Eichman[2] used another technic—that of collodion particle agglutination with acute phase serum immune globulin—and reported the following results. Collodion particles sensitized by acute phase serum were agglutinated in 73.5 per cent of tests when mixed with either source of antibody. Sera from patients with other acute infectious diseases, however, gave positive

reactions in 56.7 per cent of tests, although the titer was, in general, lower than in the sera of patients with hepatitis.

Hara and co-workers[20] in Japan have prepared a soluble antigen from the spleens of mice infected with a hepatitis strain derived from the liver of a patient who died on the 41st day of disease with acute yellow atrophy. This was inactivated by heating at 80° C and 70° C for one hour on each of two days. This antigen together with a control prepared from normal mouse spleens was tested intradermally and read at intervals for 36 hours. A positive test developed in all 31 patients tested during the 3rd or 4th week of the disease. The test was positive in 80 per cent of 67 patients with a history of previous hepatitis, in 41 per cent of 71 patients with liver disease other than hepatitis, and in 16 per cent of 77 patients with no history of hepatitis or evidence of liver disease.

Havens et al[1] prepared an antigen from feces of patients with hepatitis and also of normal persons which had the capacity to fix complement in the presence of 82.5 per cent of sera of a group of patients with viral hepatitis and with only 20 per cent of sera of normal persons. Positive reactions were also found in 50 per cent of patients with hepatic cirrhosis and in 25 per cent of patients with atypical pneumonia. Are these findings to shake our belief in the specificity of the immunologic approach?

Are we to discard all these findings in the waste basket of nonspecificity or is it high time that we modify or even discard some of our rigid concepts, rather than our findings, and adopt a more dynamic outlook to host-virus relationships?

In the epidemiologic investigations of Theiler's disease, a high prevalence of the virus in the stools of healthy carriers has been established. Could this not be the case with hepatitis? A number of viruses, such as *herpes simplex* virus, are known to remain in the host for a very long period of time. With the disturbance of certain host factors, the balance could easily be upset in favor of the virus and the host suffers. Could this not be the case with other viruses, existing in a dormant or latent phase at one time, and in an infective phase at other times? This concept finds further support in the articles which follow.

The detection in the serum hepatitis patients of an antigen in common with AHA of mice by use of the Schultz-Dale test has many practical applications. It could advantageously be used for the possible identification of icterogenic sera and in the proper choice of blood donors. In earlier studies[21], we reported on the use of cephalin flocculation test as a help in this direction. It is conceivable, however, that a latent viral agent which does not give rise to any liver damage in the host detectable by cephalin flocculation, could become active when given to another host and could result in liver damage.

The testing of blood and blood products by this technic may prove to be a very useful screening procedure for the detection of icterogenic sera and their exclusion prior to their administration to man.

In addition, I believe this technic to be an extremely helpful tool in providing an early specific diagnosis in hepatitis and other viral and rickettsial diseases.

Furthermore, it offers a very useful and "clean cut" technic for the study of antigenic relationships in viruses and rickettsial agents, a study which would

TABLE IV

A Comparative Review of Immunologic Tests in Hepatitis

Authors	Immunologic principle	Method	% Positives			
			Hepatitis	Chronic liver diseases	Pneumonia and acute infections	Healthy
Havens and Eichman[2]	Detection of antigen in serum with convalescent hepatitis or globulin as antibody.	Collodion particle agglutination	73.5	6.2	56.7	2
Havens, Lloyd, Melnick, and Colbert[1]	Detection of antibody in serum with fecal antigens.	Complement fixation	82.5	50	25	20
Hara, Kashiwagi, and Tsuchiya[20]	Detection of antibody with an antigen from spleen of mice infected with a hepatitis strain.	Skin test	100	41		16
Makari	Detection of antigen in serum with AHA of mice as antigen.	Schultz-Dale	97	56	50	16

be of the utmost importance in the understanding of diseases caused by these agents and their ultimate conquest.

Summary

1. In the human sera studied, three soluble antigens immunologically related to the ascitis-hepatitis-agents of mice (AHA) are detectable by the Schultz-Dale reaction in addition to normal liver-spleen-kidney (LSK) antigens. These are: Antigen I present in infective hepatitis (IH), Antigen II present in serum hepatitis (SH), and Antigen III found in a case of Hodgkin's disease and in a case of pneumonia with alcoholic fatty infiltration of the liver.

2. The ascitis-hepatitis-agent of mice (AHA), used to immunize guinea pigs in this study, seems to have a broad spectrum of antigenicity including all those antigens mentioned above, while a case of spontaneous jaundice in mice has Antigen I (IH) and Antigen III but is lacking in Antigen II (SH).

3. In 100 individuals tested with the Schultz-Dale Reaction for detection of hepatitis antigens, the following results are obtained:

a. All of the six cases of serum hepatitis and 18 out of 19 (i.e. 95 per cent) of the infective hepatitis cases are positive.

b. Of the eight pneumonia cases, 4 are positive (50 per cent) while five out of the nine patients with chronic liver disease (56 per cent) are positive.

c. None of the five patients with obstructive jaundice, *lupus erythematosus*, and tuberculosis is positive.

d. Of the 55 volunteers and patients from the cancer detection clinic, 9 are positive (16 per cent).

4. It is believed that this application of the Schultz-Dale reaction to detect soluble antigens in the sera of hepatitis cases, seems to be a practical and sensitive method for the diagnosis of infective hepatitis and also for the prevention of serum hepatitis. It is also very useful in the study of antigenic differences between viruses.

5. A plea for a broader and more dynamic outlook to host-viral interaction is made.

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AN IMPROVEMENT IN PROCEDURE FOR THE TUBELESS TEST FOR GASTRIC ACIDITY

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Because of the frequent association of achlorhydria or hypochlorhydria with gastric cancer, a practical screening device for determining gastric acidity would be exceedingly helpful in gastric cancer detection programs. One of the most useful methods for screening patients for the presence or absence of gastric acid is the test performed with Diagnex Blue, an azure A-resin complex[1-4]. In this test, the indicator dye is released from the ingested dye-resin complex by stomach acid, if present. The dye can be detected in the patient's urine within two hours.

As a means of simplifying the Diagnex Blue procedure, the suggestion has been made that the patient's control urine, voided prior to ingestion of the dye-resin complex, be dispensed with. The "experimental" urine voided within two hours after the dye is ingested should be employed as the control sample after appropriate chemical treatment to reduce any dye which may be present[5]. In this way, the same urine sample being tested becomes its own control and no true control urine sample need be procured prior to ingestion of the dye-resin complex.

To test the accuracy of the suggested simplified procedure, the results in 100 patients have been compared, using both a true "control" urine taken before the dye was ingested, and an "experimental control" obtained by reducing (decolorizing) the urine sample procured within two hours after the dye-resin was swallowed.

Materials and Methods

The 100 patients studied in the present investigation were seen in the Cancer Detection Clinic of Beth El Hospital, as part of the New York City Board of Health Cancer Detection Program. All were asymptomatic and were at least 40 years old. The standard methods and procedures were employed, each patient being requested to bring to the clinic both a "control" urine and a two-hour "test" urine on the day the Diagnex Blue Test was performed. The standard procedure for estimating the dye in the experimental or test urine was then followed. The control and test urines were diluted to 300 c.c. each. Two

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test tubes were filled with 10 c.c. each of control urine and a third tube with 10 c.c. of the test urine. They were then placed in a comparator supplied with the testing reagents. If the test urine was not as intense a blue as the controls, it was then acidified with one drop of 6.0 normal HCl and the three tubes were heated in a water-bath for 10 minutes and allowed to cool for two hours. They were once again placed in the comparator. When the test urine was lighter than the 0.3 mg. standard, it was considered suggestive of achlorhydria, and when the color fell between the 0.3 mg. and the 0.6 mg. standards, it was considered presumptive of hypochlorhydria.

The modified technic consisted of disposing of the control urines and filling three test tubes with 10 c.c. each of test urine. Two of these tubes were decolorized by the addition of 300 mg. of ascorbic acid and then used as the control urines. The remainder of the procedure continued exactly as in the standard method.

TABLE I

Results	Old Method	New Method
Free HCl—no boiling	15	15
Free HCl—after boiling	36	36
Hypochlorhydria after boiling	20	19
Achlorhydria after boiling	29	30
	100	100

Results

As can be noted in Table I, practically no difference was seen between the estimates of gastric acidity in this series of 100 patients when the decolorized two-hour sample of urine was employed as control and those reached with "control" urine taken before the dye was swallowed. The only discrepancy occurred with a single specimen which tested hypochlorhydric under the older method and achlorhydric when the decolorized two-hour urine was employed as the control. By either method, the patient would have been included among the group with low or absent acid requiring further study.

Comment

It is the authors' impression from this study that the newly proposed method whereby the two-hour urine sample is decolorized and then serves as its own control in the Diagnex Blue test is highly reliable. In fact, it is to be preferred, since in this procedure the concentration of soluble and insoluble material and composition of the urine will be the same for both the experimental sample and the decolorized control urine.

Of even greater importance from a mechanical point of view in a large cancer detection program, the new method requires the patient to bring in only a single urine sample, obtained after the dye has been swallowed. The procedure becomes less complicated and the patient needs less instruction. Errors through mislabeling samples are less likely to occur and the likelihood of accuracy of the final results, therefore, is enhanced.

Conclusion

In a trial with 100 patients, the Diagnex Blue test for gastric acidity has been shown to have as great accuracy when the test urine serves as its own control after decolorization with ascorbic acid as when a separate sample of urine, taken before the dye is swallowed, serves as the control.

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POWDERED DUODENAL EXTRACT IN THE TREATMENT OF PEPTIC ULCER

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Introduction

In medicine, few diseases have been so thoroughly explored and yet so little understood as have been peptic ulceration and ulcerative colitis. The books, papers and articles written on these two conditions are voluminous; the list of drugs giving "good to excellent results" are even more impressive if volume is taken as sole criterion. Even at this enlightened period of space travel, we still do not have a ready explanation regarding the cause, precipitating factors or apparent, spontaneous relapses or remissions as seen in these diseases. One thing is certain, both conditions are intricately related to their host's psyche, and thus represent two of the so-called "psychosomatic" illnesses.

As with most of these diseases, very few specific treatments exist. Hence, various antacids, antispasmodics, sedatives, etc., are used in the management of these cases with more or less subjective and occasionally objective improvement. Any new substance suggested for the treatment of these patients will, therefore, be readily accepted and tried. Hence, when it was brought to our attention that several authorities in the field of gastroenterology had reported good to excellent results with the use of a hog's duodenal extract for the treatment of these two conditions[1-5], we decided to try this product in a series of our cases. The rationale behind the use of this preparation stems from the observation that the gastrointestinal mucosa is endowed with a substance whose function is to protect the mucosa from autolysis by proteolytic enzymes contained in the juice. This antiproteolytic factor appears to be most prolific in the stomach and small intestine. Duodenal extract powder* as used by us is not only rich in this factor, but also in enterogastrone, a hormone derived from the duodenal mucosa which acts upon the stomach, reducing its motility and acid production[6,7]. In addition, Sandweiss[8] has shown that the upper small intestine not only contains enterogastrone, but also an antiulcer factor similar to anthelone in the urine. Ivy et al[7] also described a procedure whereby they were able to prevent histamine stimulation of gastric acid secretion by the intravenous injection of an extract of the upper intestinal mucosa into dogs. He also found that the ulcers which untreated

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*Viodenum, manufactured by the VioBin Corporation, Monticello, Ill. and supplied gratis to us in tablets containing 0.5 gm. of the active material.

Mann-Williamson dogs routinely develop were prevented by this preparation and further that once discontinued, the onset of ulceration was much more prolonged than that following discontinuance of antacids. Finally, Anderson et al[6], using 7 per cent alcohol as a stimulant for mucus secretion, reported that the concentration of mucus in aspirated samples was markedly lower in duodenal ulcer patients than in normal individuals. After treating the duodenal ulcer patients with a preparation of hog mucin orally for several months, the concentration of mucin in alcohol-stimulated juice rose to normal levels. It was his, as well as Ivy's[6] and others' observations that the ulcer patient secretes less mucus than does the normal person.

Materials and Methods

We followed 33 cases of peptic ulcer for a minimum of one month in three cases to a maximum of over a year in several others. The study was extended over a two-year period but the first nine cases collected either failed to return to clinic following several visits or required surgery before this two-year study was completed. We also treated seven cases of ulcerative colitis and followed them regularly; they, however, are not included in this report due to the small number. Of the peptic ulcers, 30 were duodenal, two gastric and one combined gastric and duodenal. Ten gave a past history of previous upper gastrointestinal bleeding. Approximately one-half gave a past history of intractability, that is, continuing epigastric distress in spite of medical management. It was not always possible, however, to establish with reasonable certainty that the patient had been closely following his prescribed course of therapy.

Each patient had a complete history and physical examination, routine urine and blood count, barium meal and then special tests when indicated. Follow-up gastrointestinal studies were done in most of them, usually while attending the Gastrointestinal Out-Patient Clinic. The gastric ulcers, in addition to having more frequent barium studies, also had one or more gastroscopic studies. Most of them also had gastric acidity studies, although a few refused this procedure. In all but two cases, the regimen that was followed in the Out-Patient Clinic was begun while they were still in the hospital. It was simple and consisted of the administration of, initially, one Viodenum tablet, three times a day and two at bedtime, plus a free reign of diet. They ate the usual three instead of six meals a day and were asked only to refrain from exceptionally spicy foods and alcohol. It was soon learned that most did better on two or three Viodenum tablets, three times a day and at bedtime. In addition to the Viodenum, they were given tincture of belladonna to take at the first indication of epigastric pain and to repeat if the pain persisted. When the pain subsided, it was discontinued and not taken again until, or unless, the pain recurred. They were seen regularly in the clinic by one of us (T.K.C.) and usually at two-week intervals. On each visit, they were asked about abdominal discomfort, evidence of bleeding and nausea or vomiting. In addition, the interviewer attempted to elicit any symp-

TABLE I

CASE SUMMARY TABLE*

Case		Age	Mos. treated	Evaluation of treatment
1	J.M.	47	3	Doing well, stopped visits. Surgery 33 weeks later for recurrent epigastric distress.
2	W.L.	35	6.5	Did well initially. Missed visits. Restarted on Viodenum with poor results. To surgery.
3	J.B.	50	15.5	Bled while on treatment.
4	J.H.	30	10.5	Surgery for intractability.
5	E.H.	62	12	Surgery for bleeding and perforation.
6	S.H.	25	10	Surgery for partial obstruction.
7	C.B.	66	18	Fewer recurrences of less severity.
8	L.S.	35	8	Surgery for pyloric obstruction.
9	R.K.	42	1.5	Surgery for penetrating ulcer.
10	Y.S.	51	6	Same number and severity of recurrences.
11	M.M.	53	11	Asymptomatic.
12	E.M.	44	5	Fewer recurrences.
13	F.S.	37	10.5	Fewer recurrences of less severity.
14	F.W.	27	9.5	Fewer recurrences of less severity.
15	E.D.	69	10.5	Asymptomatic.
16	H.S.	38	3	Asymptomatic.
17	C.O.	?	6.5	Asymptomatic.
18	N.G.	24	6	Fewer, less severe recurrences.
19	T.C.	47	4.5	Fewer, less severe recurrences.
20	V.W.	47	5	Same number and severity of recurrences.
21	A.W.	15	3	Fewer, less severe recurrences.
22	R.H.	60	2	Slight decrease in abdominal symptoms. Expired with chronic renal failure.
23	V.E.	42	2	Symptoms cleared during short period of observation.
24	W.B.	41	1	Some decrease in symptoms during short period of observation.
25	J.W.	51	1	Asymptomatic during short period of observation.
26	J.J.	44	4	Did well then stopped his clinic visits.
27	E.W.	38	2	Did well during the short period of observation.
28	J.W.	50	1	Did well. Stopped his visits because he was "feeling fine".
29	W.B.	39	4	Did poorly. Surgery for intractability.
30	J.S.	42	5	Initially, all abdominal symptoms eliminated. However, pain recurred and surgery was performed.
31	B.G.	68	5	Duodenal diverticulum. No relief of symptoms.

*Two observed less than one month.

toms suggesting an adverse side reaction of the drug. If they seemed to be doing poorly, the Viodenum was gradually increased up to a maximum of 14 to 16 tablets daily. If symptoms persisted at this level, either regular doses of belladonna were prescribed along with the tablets or they were taken off the hog mucosal extract altogether and switched to the usual antacids-antispasmodics. Every effort was made not to build this drug up to the patient. To most of them, it was simply one of the many different "pills" that had been prescribed during the course of their illness.

Finally, in an attempt to rule out completely the psychologic error always to be reckoned with in evaluating the treatment of a disease especially in the so-called psychosomatic group, a double-blind study was done, giving alternately "preparation A" to one-half the group and "preparation B" to the other half. Both these preparations looked exactly alike and also were identical in appearance to the original standard tablet. The observer too did not know which tablet contained the active ingredient until the termination of the study.

The 33 cases of proven peptic ulcer were studied from the standpoint of symptoms suggestive of continued or recurrent ulcerative activity, complications and undesirable drug side-effects or toxicity.

Results

Most patients initially did very nicely, some commenting that this was the best they had felt since the beginning of their illness. About 90 per cent of them felt well while they maintained themselves on two tablets before meals and at bedtime. Several patients that were resistant to good medical treatment previously became asymptomatic on this substance (see case reports). Nine cases, however, subsequently required surgery (Table I).

The double-blind study revealed better control of the symptoms with the drug as compared to the placebo.

Case Reports

1. F.W., a 27-year old white male, had noticed occasional epigastric distress following bouts of drinking for the past year. He was not a heavy drinker, limiting his indulgences to the week-ends. Two months prior to hospital admission, the epigastric distress became persistent and he experienced one episode of hematemesis.

A barium meal revealed a deformed duodenal bulb. There was no ulcer crater seen. He was started on Viodenum in the hospital and then discharged. Since then he has done nicely on this medicine alone, taking eight tablets daily, i.e. two, three times daily and at bedtime.

2. H.S., a 38-year old white female, gave a three-year history of epigastric distress relieved by baking soda and milk. Barium meal showed a duodenal

deformity. She was started on Viodenum and offered the statement some months later that she "felt better on this medicine than anytime in the past six months". There was one bout of epigastric distress early in the course of treatment, quickly relieved by the addition of tr. belladonna. Unfortunately, she did not return to clinic after a little over three months of observation.

3. C.O., a middle aged colored female, gave a history of recurrent epigastric distress for the past seven years. There was a definite pain-food-relief pattern. Then, two weeks prior to hospital admission, she passed several black stools. She was not on iron medication at the time. Barium meal revealed a prepyloric ulcer niche. She was started on Viodenum alone and from then to the termination of our period of observation (6.5 months) we could elicit no abdominal complaints.

Comment

Flood[9,10], in studying a group of 233 patients upon which he hoped to accumulate data to serve as a basis for comparison with results of surgical treatment and for reference in the evaluation of newly proposed remedies for peptic ulcer, came to the conclusion that once the ulcer is healed, medical treatment probably has little influence on the natural course of the disease. The majority of his patients ultimately relapsed. Most of these patients were initially hospitalized and underwent intensive antiulcer therapy. He found that the majority of his patients with uncomplicated ulcers get prompt and complete relief after institution of medical treatment. This has also been our experience. The pain frequently disappears within a day and almost always within a week after hospitalization. He found the healing time for both duodenal and gastric ulcers to be about six weeks. The most striking feature of his article was the incidence of recurrence of symptoms in peptic ulceration after initial intensive hospital treatment. It averaged once every 2.1 years for the duodenal and once every 2.4 years for the gastric ulcers. This asymptomatic period is considerably longer than that of most other reported series of cases. The criteria for recurrence of symptoms, however, varies with different authors, some including any epigastric distress of whatever magnitude as incidence of recurrence, others demanding more dramatic symptoms before classifying them as a recurrence. In this series, any occurrence of epigastric pain, other than occasional vague, "nausea" or "indigestion" was classified as recurrence. Raimondi, et al[11], in studying 151 patients for a period of one to two and three-quarter years, found that the majority of patients treated and observed for two years or more had multiple recurrences. They agreed with Flood that treatment of the symptoms of active ulcer is very satisfactory but, as in our cases, found the chief therapeutic problem was prevention of the high incidence of recurrences. Marshall[12], in treating 1,000 cases, used intensive initial therapy—every hour—with large doses of aluminum hydroxide, calcium carbonate and magnesium oxide along with atropine and phenobarbital. After this early heavy dose, he reduced the fre-

quency and carried them on a modified regimen for another four to six months. He then allowed them to go back to their preulcer routine, including an unrestricted diet. He believes in this way the patient is better able to re-experience his previous symptoms at an early stage in the reopening of the ulcer crater and should then again be put back through the original therapeutic routine with intensive therapy. Crayer[13], found no difference in the recurrence rate or number of complications in two groups of patients, one of which adhered rigidly to their diet, the other which did not.

In reviewing the literature and in our own experience, we found that statements regarding the efficacy of a new drug based on dramatic, but short-term, results are not only unwise but can be most misleading to those who take them at their face value. These patients are quite suggestive and respond initially with a marked decrease of symptoms to almost anything new that is given to them. Sooner or later, however, the symptoms recur, frustrating both patient and physician. No drug should be accepted for the treatment of this condition until it has proven itself over a substantial period of time and also been subjected to careful double-blind studies. Because of this idea, Viodenum was subjected to a critical evaluation for about two years. The results indicated a good initial response and a long-term response somewhat better than that reported with the use of the presently available antacids in conjunction with antispasmodics. Also, many of the reports claiming dramatic improvement with these drugs were not critically analyzed by a double-blind study.

Side-effects

Clinically, there were no untoward effects and only two patients admitted to occasional mild episodes of nausea after taking the tablets. This usually occurred in the morning prior to breakfast.

Summary and Conclusions

Several reports were alluded to claiming good to excellent results with the use of hog's mucosal extract for the treatment of peptic ulcer and ulcerative colitis. The preparation did not attain general popularity at the time, apparently because of its unpalatability.

The tablet form, however, which we used, is not at all unpleasant to take.

The results suggest that this preparation is at least as good as the currently popular antacids and antispasmodics and has no toxic or side-effects.

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THE USE OF A CARBON DIOXIDE-PRODUCING SUPPOSITORY AS A SUBSTITUTE FOR THE ENEMA

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Very few hospitalized bed patients have spontaneous bowel movements. Those who have been troubled with constipation before admission may become severely obstipated while in the hospital. Unrelieved constipation may lead to fecal impaction, frequently a serious problem in the aged and debilitated individuals. In every department of a general hospital, efforts are made at appropriate intervals to assist the patient in evacuating the bowels. From time immemorial enemas containing oil or soap suds, or so-called high colonic irrigations have been utilized for this purpose. The enema has many disadvantages. Some patients resent it. It may be ineffective and have to be repeated. It may not be completely evacuated, cause tenesmus and frequent requests for the bedpan. Air may be introduced, retained in the colon and cause intestinal colic. The irritation of soap suds may produce a burning discomfort in the anal area. Administration of enemas increases the demands on the time of the nursing personnel. The nursing shortage is an ever increasing problem in all hospitals. A simple, inexpensive, less time-consuming method of aiding bowel evacuation would therefore be very advantageous. In the search for such a method it would clarify the problem to briefly review the mechanism of defecation and causes of constipation.

Physiology of Defecation and Constipation

Motor activity of the colon is minimal except during the act of defecation. Feces accumulates in the sigmoid colon where it is usually retained because of the narrowed, angulated rectosigmoid junction. Although an anatomic sphincter is not present at this site, it is probable that a physiologic sphincteric mechanism does exist which also aids in making the sigmoid colon the reservoir for feces before the act of defecation. According to the conditioning of the human, and usually after a particular meal, mass peristaltic waves occur in the colon as a result of a gastrocolic reflex, the rectosigmoid junction is relaxed,

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and feces is carried into the rectum. Sudden distention of the rectum reflexly creates the desire to defecate, wherein peristalsis in the colon increases, the abdominal and levator ani muscles contract, the anal sphincters relax, and the rectum is evacuated. The frequency, quantity and consistency of the normal bowel movement varies with the habit of the individual and the type of food ingested. Thus normal bowel evacuations may occur from 1 to 3 times daily, or only once every 2 or 3 days. Examination following a normal elimination should disclose an empty rectum.

Constipation may be defined as a change in the usual bowel habit of an individual where there is either a delay in the evacuation of feces, the passage of hard stools, excessive straining to evacuate the stool, or a combination of these features. Many types and causes of constipation are described. But if one can exclude organic disease of the colon and the unstable colon, chronic constipation is frequently found to be caused by the loss of the normal defecation reflex. As a result of habitual neglect, or the frequent use of cathartics and enemas, or the slow filling of the rectum as may occur in redundant colons, the rectal reflex is impaired and feces accumulates in the rectum. The rectum may empty inadequately, so that after evacuation examination discloses a large amount of retained feces. An evacuation may not occur for many days, resulting at times in hardening and impaction of the feces. Occasionally fecal impaction is overlooked because frequent loose movements may be passed around a mass of hard feces which is retained in the rectum. Hurst[1] has classified this type of rectal constipation as dyschezia. One of us[2] found that this type of constipation so distended the rectums of soldiers in combat, that the incidence of rectal perforation by bullets and shell fragments was greatly increased. A more acute form of this type of constipation occurs in otherwise normal people who have been hospitalized and confined to bed because of medical disease, operative procedures or childbirth. Inactivity, restriction of diet, the use of constipating drugs and fear of pain on the part of the patient prevent the normal evacuation and, as the rectum remains filled, the defecation reflex is inhibited. The use of enemas and cathartics initiates a chain of events which may ultimately lead to the development of chronic rectal constipation.

Material and Method

We have studied the effectiveness of a rectal suppository* which generates a harmless gas when it comes into contact with the humid rectal mucosa. The composition of this suppository is as follows:

Sodium bicarbonate	0.6 g.
Potassium bitartrate	0.9 g.
Calcium silicate	0.05 g.

*Pharmalax Suppository, supplied by Pharmacia Laboratories, Inc., N. Y.

Bentonite USPxiii	0.3 g.
Polyethylene glycol	0.2 g.
Dextran (282)	0.05 g.
Cocoa butter	0.05 g.
Vegetable lecithin	0.1 g.
Talc	q.s.

The bicarbonate of soda and potassium bitartrate, in the presence of moisture, react to produce carbon dioxide. If an adequate amount of gas is generated to distend the rectum and induce a normal defecation reflex, without causing undue discomfort or irritation, a physiologic response and normal bowel movement ensues. Geo[3], von Friesen[4], Banner[5], Hilden[6], Briggs and Leighton[7], Bolton and Benson[8] have observed the usefulness of this suppository as a substitute for the enema in many women during the postpartum period. Hehrne[9] has found it to be of value for the treatment of uncleanliness in mental patients. Snellman and Heidenberg[10] use it effectively in the treatment of patients before and after anal operations. Rosenfeld, Bogdanski and Goldner[11] have found it efficacious in producing a bowel evacuation after the feces has been kept soft by the combination of a wetting agent and cathartic. Among the chronically ill, their regimen has practically eliminated fecal impaction and the need for enemas. Bernstrup[12] felt that it was of no value in emptying the colon before x-ray investigation.

The suppository is easily introduced either dry or slightly moistened with water. At the start of our investigation, one suppository was used. If a beneficial effect was not obtained within a half hour a second one was introduced. The need for the use of 2 suppositories was so frequent that in most of our cases both were introduced at the same time. Among 150 medical cases, 90 had adequate and 60 inadequate bowel evacuations. Among 50 postoperative cases, 33 had adequate and 17 inadequate evacuations. Twenty-five patients were prepared for proctosigmoidoscopy with no other medication than 2 suppositories administered 1 to 2 hours before the examination. Eleven retained enough feces in the rectum to prevent adequate observation. In 6 the rectum was empty, permitting adequate proctoscopy, but the sigmoid contained some feces so that it could not be examined completely. In 8 patients the sigmoidoscope was passed for a distance of 10 inches without encountering any feces, permitting complete proctosigmoidoscopic examinations. In all cases the mucosa showed no untoward effect caused by the suppository or carbon dioxide. Barium enema x-ray studies were performed in the latter group of 8 patients. In all, fecal masses were noted in the more proximal portions of the colon which interfered with adequate visualization and interpretation of the roentgenograms. In general among all patients studied, it was found that the response was far better among those who had not suffered from chronic constipation prior to hospitalization.

Summary and Conclusions

1. The use of a carbon dioxide-producing suppository in evacuating the bowel is described.

2. The physiology of defecation and constipation is briefly reviewed.

3. The suppositories were effective in 62 per cent of hospitalized medical and postoperative bed confined patients.

4. The suppositories were used to prepare 25 patients for endoscopic examination of the lower bowel; 32 per cent were adequately sigmoidoscoped and an additional 24 per cent were adequately proctoscoped.

5. The colons of 8 patients whose rectosigmoid regions were completely clean at the time of proctosigmoidoscopy, contained fecal matter when barium enema x-ray examination was performed. The suppository is therefore of no value in preparing the colon for roentgen study.

6. There was no demonstrable untoward reaction on the mucous membrane of the rectosigmoid colon by the suppository itself or the carbon dioxide which it produces.

7. The gas-producing suppository can act as a substitute for the enema in a majority of hospitalized patients. Suppositories capable of producing more gas, thus distending the rectum even more, may increase the number of successful results.

8. Such a suppository does not impose upon the time of the nursing staff, minimizes the discomfort of the patient by replacing the enema, and results in financial saving to the hospital.

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ABSTRACTS FOR GASTROENTEROLOGISTS

ESOPHAGUS

ESOPHAGEAL STRICTURES AFTER GASTRIC SURGERY AND NASOGASTRIC INTUBATION: J. A. W. Bingham. Brit. M. J. 5100:817 (4 Oct.), 1958.

The occasional development of an esophageal stricture without apaprent cause following the use of an indwelling nasal suction is worthy of note. The mechanism for the production of these strictures has not been discussed at length. The author studied this complication in four patients and from his observations has arrived at some definite conclusions. He believes that a reflux esophagitis associated with a hiatus hernia is the basis for the stricture formation. The recumbent position accentuates the potentiality for the development of a stricture and for this reason he advocates the avoidance of this position if possible.

BERNARD J. FICARRA

ESOPHAGEAL STENOSIS AFTER PARTIAL GASTRECTOMY: K. C. McKeown. Brit. M. J. 5100:819 (4 Oct.), 1958.

The formation of esophageal stenosis following gastrectomy is discussed by the author. The most interesting aspect of his discussion revolves about the etiology of this complication. The various theories presented are a possible thrombophlebitis extending from the coronary vein upwards along the esophageal tributaries and causing inflammatory changes in the wall of the esophagus. Another possibility is that the left gastric artery might have been ligated too high producing an ischemia of the lower esophagus with a subsequent stenosis formation. Infection in the lower esophagus may be another cause for this stenosis. Another factor may be the trauma resulting from an indwelling tube. Treatment for this condition is conservative with dilatation performed when necessary.

BERNARD J. FICARRA

INTESTINES

ANOGENITAL PRURITUS: Murry M. Robinson. Am. J. Proct. 9:361 (Oct.), 1958.

Anogenital pruritus is difficult to treat because the etiology is nonspecific in most cases. Where a specific cause is found, the results are good, but so many have altered

appearance due to scratching and medication that empiric treatment is relied upon. However, pinworms, neoplasms, local disease, gout and diabetes should be looked for.

Conventional therapy includes local anesthetics of the "caine" variety, which frequently sensitizes the skin and leads to contact dermatitis; antihistamines which also cause dermatitis in 6-10 per cent of cases; coal tar and fatty acids; superficial x-ray therapy, good as a last resort only; and, cortisone and the newer steroids, which have given the best results thus far.

To test the value of medicaments, 34 patients were divided into 4 groups, and hydrocortisone, fludrocortisone, crude coal tar, and a mixture of the last two, were given to each group. All patients on steroids did well, but the best results were obtained in the group using crude coal tar, chlorhydroxyquinoline, and fludrocortisone. The severity of the pruritus and the objective lessening of the skin lesions was noted. Of interest, the patient with no skin lesion, did not respond. No untoward reaction was encountered from the use of steroids topically.

NORMAN L. FREUND

AVOIDING COLOSTOMY IN COLON SURGERY: Alexander Solosko. Am. J. Proct. 9:385 (Oct.), 1958.

In spite of cheerful reports to the contrary, many colostomy patients are social recluses and are miserable people. Many of these cases could have been treated by anterior resection making the colostomy unnecessary. The over all results are just as good in this operation, as in the Miles procedure, and to prove this point, the statistics of Babcock, Bacon, and Best are quoted. The author advocates anterior resection for all lesions lying above 5 cm. from the anorectal line.

Avoidance of colostomy can also be accomplished when temporary measures are being instituted, by performing "internal colostomy", such as ileocolostomy or ileosigmoidostomy, as a by-pass operation. In terminal patients with advanced disease, nothing is done, but the patient carried on morphine until the end.

NORMAN L. FREUND

ANORECTAL AND RELATED FISTULAS: D. O. Janes. Am. J. Proct. 9:392 (Oct.), 1958.

In outline form the author lists the important features of anorectal fistulas. They occur from 20 to 60 years of age, males predominantly, and represent 25 per cent of anorectal disease. Etiology may be congenital, from surrounding viscera, disease of the bowel, or infection from the crypts of Morgagni.

Symptoms are discharge and pruritus ani, following an abscess that has ruptured sometime previously, or was drained surgically. The anatomy of the sphincters is most meagerly given. Treatment consists of opening all tracts and saucerizing the wounds. Rectovaginal, rectourethral and colonic fistulas are also mentioned in brief.

NORMAN L. FREUND

PERFORATION OF THE CECUM COMPLICATING ADYNAMIC ILEUS: W. G. Eckman, Frank Wenzke and William Abramson. Am. J. Surg. 96:718 (Nov.), 1958.

Perforation of the cecum is a serious complication, usually of distal obstruction of the large bowel. The mortality rate reported by Wangensteen is approximately 35 per cent. Perforation of the cecum in instances of paralytic (adynamic) ileus is uncommon.

A case report is given of a woman 75

years of age, who died of perforation of the cecum in spite of aggressive treatment to decompress the small intestines by conservative measures. The perforation occurred while the Levin tube was draining satisfactorily. The pathological report showed peritonitis as a result of perforation of the cecum. There was no evidence of any distal obstruction in the large intestine.

Management of cecal perforation is best performed by emergency laparotomy and cecostomy. The approximate intramural pressure necessary for perforation of the cecum has been estimated by Wangensteen to be approximately 26 cm. of water. While this measurement has been made only in patients suffering from distal organic obstruction, Wangensteen mentions that in paralytic ileus one might expect high cecal pressure. Some authors believe that a cecum of 9 cm. or over in greatest transverse diameter as shown by x-ray, is indicative of impending perforation.

It is important and worthy of emphasis, that elective cecostomy be performed in any patient in whom the cecal measurement approaches 9 cm. in transverse diameter.

CARL J. DEPRIZIO

LIVER AND BILIARY TRACT

A STUDY OF HEART DISEASE IN ONE HUNDRED EIGHT HOSPITALIZED PATIENTS DYING WITH PORTAL CIRRHOSIS: John H. Lunseth, Edwin G. Olmstead and Francis Abboud. A.M.A. Arch. Int. Med. 102:405 (Sept.), 1958.

Several previous studies reported in the literature have made the statement that hypertension and coronary arteriosclerosis are less common in patients with hepatic cirrhosis than in those without such liver disease. Therefore, 108 consecutive patients dying of portal cirrhosis were studied at autopsy for cardiac abnormalities. Fifty-two of them had serious associated cardiac disease. Such findings speak against an ameliorating effect of cirrhosis on the heart. Among those patients, however, were only 40 with hypertensive, arteriosclerotic or valvular disease while 12 had idiopathic cardiomegaly only. The latter manifested itself clinically by chronic progressive congestive heart failure, with or without nonspecific murmurs and electrocardiographic changes and marked muscular hypertrophy with mild focal fibrosis and myocarditis. It is suggested that idiopathic hypertrophy of the heart is caused by hemodynamic and nutritional changes caused by the hepatic cirrhosis and that cirrhotics suffer from this entity in addition to the common types of heart disease.

H. B. EISENSTADT

BILIARY CIRRHOSIS: H. E. MacMahon. A.M.A. Arch. Int. Med. 102:841 (Nov.), 1958.

Originally the name of biliary cirrhosis was attached to the late changes of the liver following prolonged obstruction of the external bile passages. However, during recent years 7 different forms of chronic parenchymal liver changes following malfunction of the bile duct system have been distinguished. It is possible that additional types may be discovered in the future. The 7 different forms of biliary cirrhosis are: 1. Obstructive biliary cirrhosis due to external bile duct obstruction. 2. Cholangiolitic biliary cirrhosis due to inflammation of the cholangioles. 3. Pericholangiolitic biliary cirrhosis characterized by chronic granulomatous periportal inflammation causing obstruction of the small bile ducts. This form occurs most often in middle-aged females and is frequently associated with hypercholesteremic xanthomatosis. 4. Acholangic biliary cirrhosis of infants and children due to congenital bile duct stenosis or atresia. 5. Fibroxanthomatous biliary cirrhosis, a rare disease of very young children associated with reticuloendotheliosis. 6. Biliary cirrhosis associated with cystic fibrosis of the pancreas. 7. Carcinomatous biliary cirrhosis due to metastatic lymphangitic involvement of the liver.

H. B. EISENSTADT

OBSTRUCTIVE JAUNDICE AND EXTRAHEPATIC PORTAL HYPERTENSION WITH EMPHASIS ON THE HAZARD OF SURGICAL EXPLORATION: George M. Johnson. J. Indiana State M. A. p. 1537 (Nov.), 1958.

Jaundice is rarely present in proved extrahepatic portal vein obstruction, although minimal jaundice is frequently observed in portal cirrhosis with associated portal hypertension.

The author presents two case reports in which obstructive jaundice was present in extrahepatic portal hypertension.

On autopsy after unsuccessful operation on the 1st case, the portal venous system was found dilated throughout and approximately 4 cm. from the liver the vein narrowed into a solid cord. Gross sections through the cord revealed no lumen. Sections of the liver revealed the presence of bile thrombi plugging the bile canaliculi, particularly in the central area with findings being compatible with those of biliary obstruction rather than that of hepatitis. The final conclusion was that of congenital obliteration of the portal vein. The jaundice was obstructive in type but the exact cause not determined. However, it was conjectured that intermittent jaundice occurred from occlusion of the common bile duct by extrinsic pressure from the obstructed portal vein.

Surgery on the 2nd patient was successful with the disappearance of the jaundice. Biopsy of the liver which was taken at the time of his surgery revealed many bile canaliculi that were filled with dense pigment material producing a pattern characteristic of bile duct obstruction. There was no indication of hepatitis or cirrhosis. Five months later jaundice again occurred with spontaneous recovery. It was concluded that there was extrahepatic obstruction of the portal vein of congenital origin with intermittent episodes of obstructive jaundice with undetermined etiology.

JOSEPH E. WALTHER

BOOK REVIEWS FOR GASTROENTEROLOGISTS

THERAPEUTIC RADIOLOGY, RATIONALE, TECHNIC, RESULTS: William T. Moss, M.D., Assistant Professor of Radiology, Northwestern University School of Medicine, Department of Radiology, Chicago, Ill.; Director, Department of Therapeutic Radiology, Chicago Wesley Memorial Hospital; Chief, Department of Therapeutic Radiology, Veterans Administration Research Hospital, Chicago, Ill., with foreword by Lauren V. Ackerman, M.D. 403 pages, 146 illustrations. C. V. Mosby Co., St. Louis, Mo., 1959. Price $12.50.

Dr. Moss has written a very rational and comprehensive treatise on "Therapeutic Radiology". The entire body is covered, treatment is outlined, discussed in detail, indications and contraindications and results are shown.

The illustrations, printing, references and index are complete. Radiologists, as well as surgeons, whatever specialty they practice, will find this valuable text of great help.

DIFFERENTIAL DIAGNOSIS OF INTERNAL MEDCINE—A COMPREHENSIVE DISCUSSION FOR PHYSICIAN AND MEDICAL STUDENTS: By Dr. Robert Hegglin, Professor of Medicine, University of Zurich; Director of the University Poliklinic. Sixth Revised and Enlarged Edition. 819 pages, 517 illustrations, many in color. Georg Thieme Verlag, Stuttgart, Germany, 1959. Price $18.85.

The reviewer is acquainted with several of the previous editions of Dr. Hegglin's Differential Diagnosis, however, this 1959 volume is brought up to date and supersedes all others. Diagnosis and differential diagnosis is stressed and the beautiful illustrations, especially in color, add greatly to the value of the text.

The only criticism one can find is that there are too many syndromes named after clinicians which whom many of us in the United States are unfamiliar. This should not, however, detract from the value of the book.

An extensive reference and index complete the volume.

Those of us who read German will find Dr. Hegglin's text a valuable *vademecum*.

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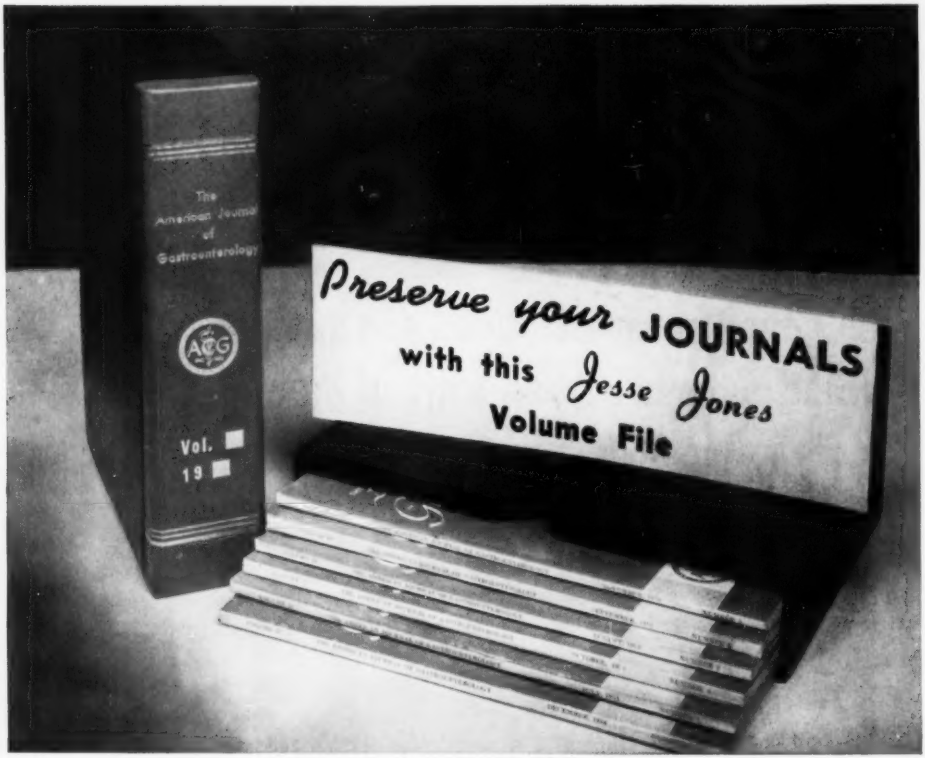

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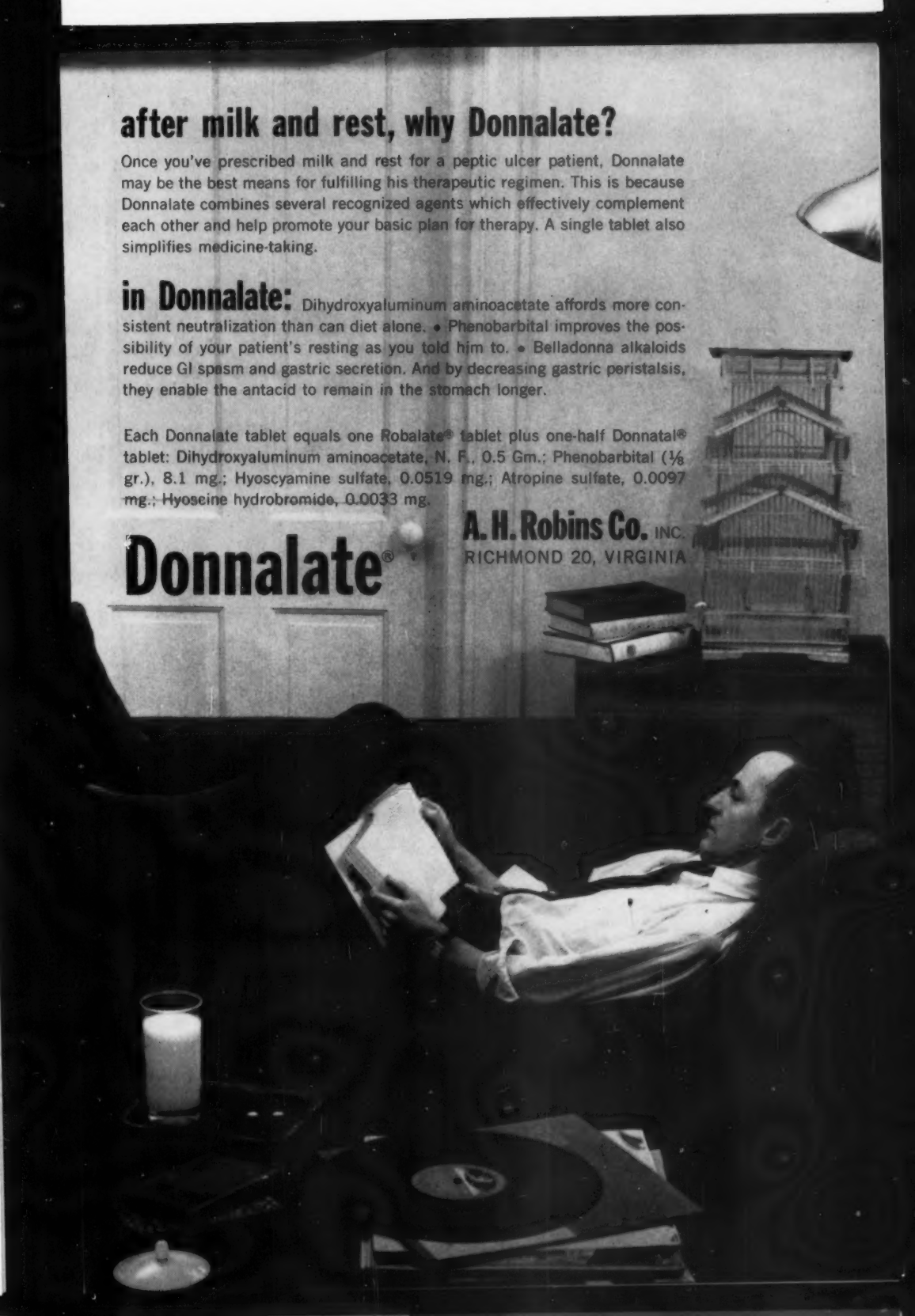

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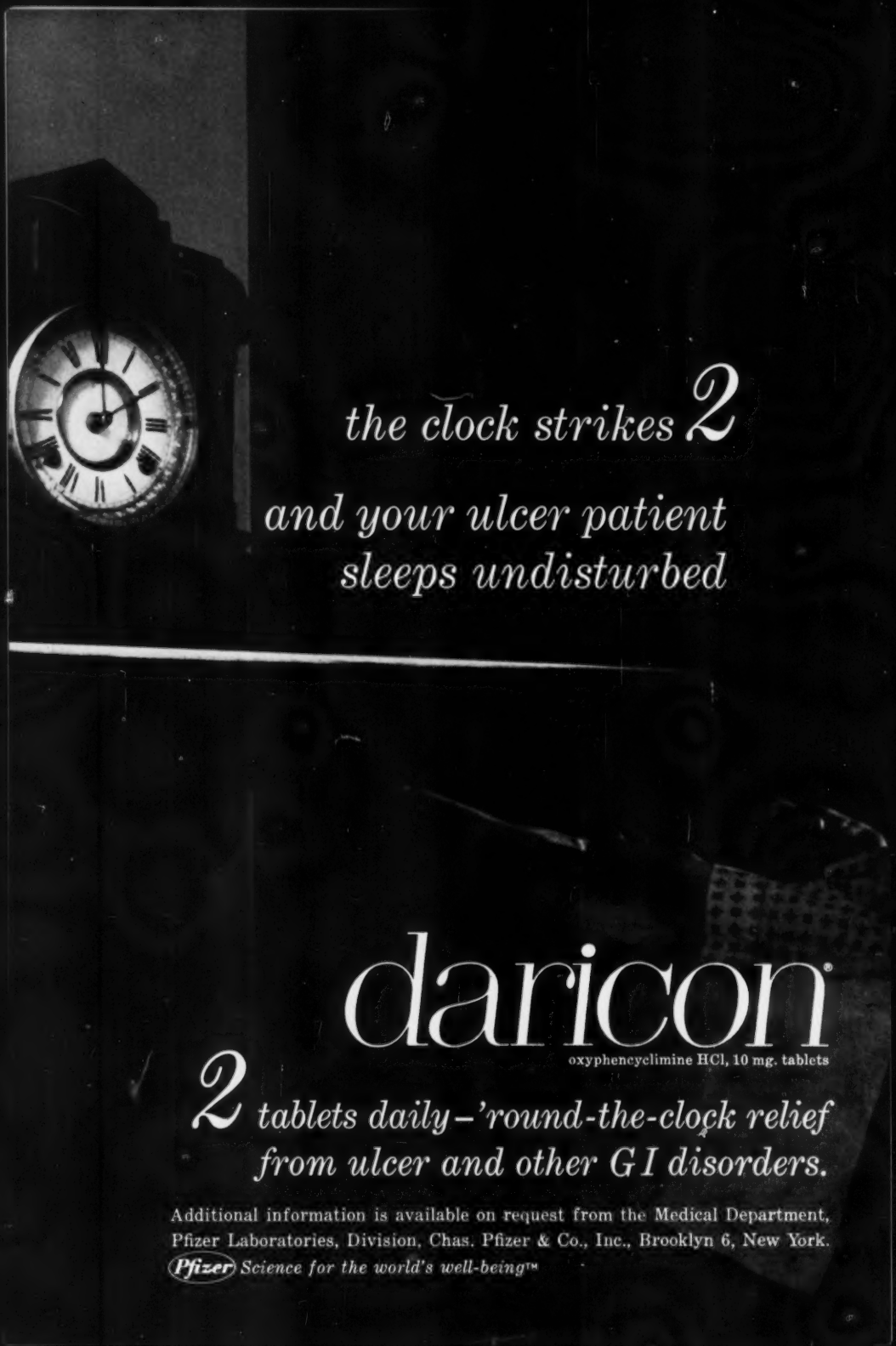
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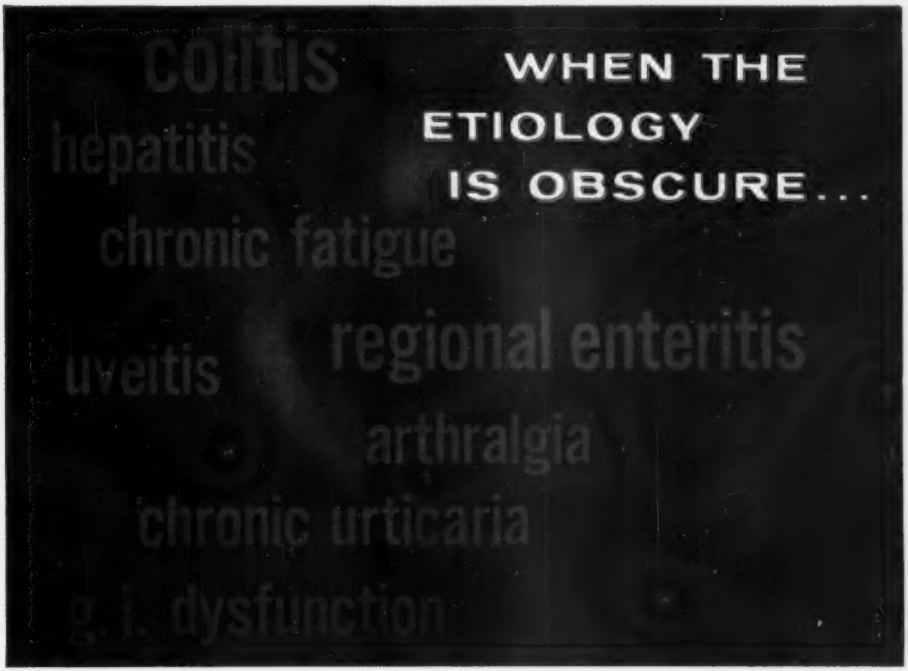

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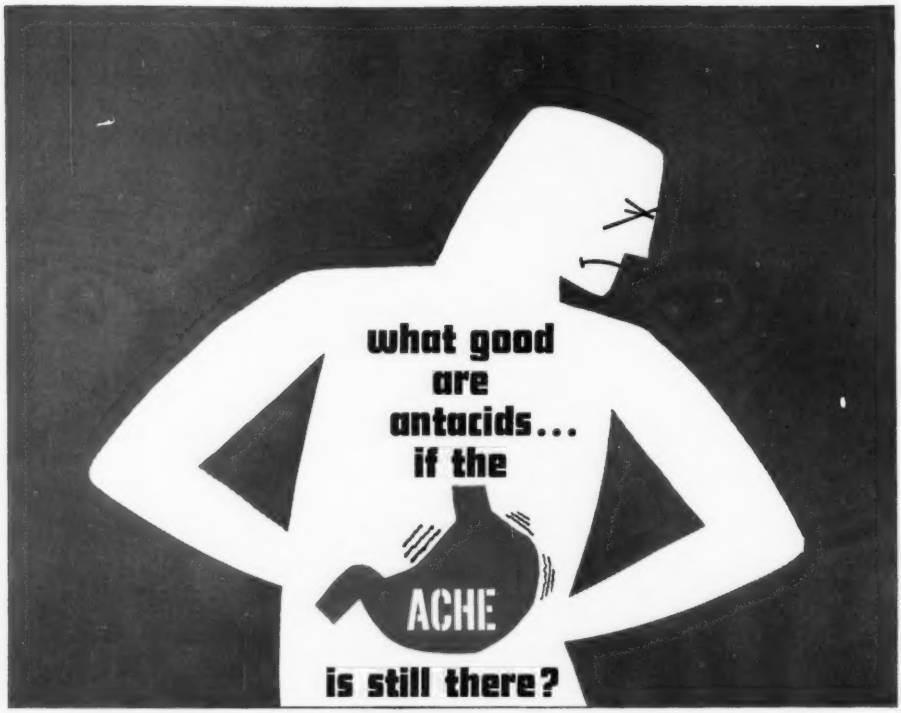

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